# CENTER FOR DRUG EVALUATION AND RESEARCH

# APPROVAL PACKAGE FOR:

# APPLICATION NUMBER
# 21-169

## Statistical Review(s)

# Statistical Review and Evaluation

| | |
|---|---|
| **NDA**: | 21-169 |
| **Drug Name**: | REMINYL (galantamine) |
| **Indication**: | Alzheimer's Disease |
| **Sponsor**: | Janssen Research Foundation |
| **Studies Reviewed:** | GAL-INT-1, GAL-USA-1 and GAL-USA-10 |
| **Clinical Reviewer**: | Rangit Mani, M.D. (HFD-120) |



## 1. Introduction

Alzheimer's disease, the most common and important degenerative disease of the brain, is characterized by clumps of neurofibrils and microscopic brain lesions and by confusion, disorientation, memory failure, and speech disturbances, and resulting in progressive loss of mental capacity.

The sponsor developed REMINYL (galantamine) for the symptomatic treatment of Alzheimer's disease. The submission of this NDA 21-169 includes 3 primary studies, and 9 supportive studies. In the current review, three primary studies, GAL-INT-1, GAL-USA-1, and GAL-USA-10 will be discussed.

- **GAL-INT-1** was a 6-month, double-blind, placebo-controlled, parallel study comparing fixed doses of galantamine 12 mg bid or 16 mg bid with placebo conducted at Canada and seven European countries with 653 patients randomized.
- **GAL-USA-1** was a 6-month, double-blind, placebo-controlled, parallel study comparing fixed doses of galantamine 12 mg bid or 16 mg bid with placebo conducted at 33 centers in U.S.A. with 636 patients randomized.
- **GAL-USA-10** was a 5-month, double-blind, placebo-controlled, parallel study comparing 4 mg bid, 8 mg bid, or 12 mg bid of galantamine using a slow-titration regimen with placebo conducted at 54 centers in U.S.A. with 979 patients randomized.

## 2. GAL-INT-1

### 2.1. Objective

The primary objective was to evaluate the efficacy, safety and tolerability of galantamine in patients with Alzheimer's disease.

## 2.2. Study Design

GAL-INT-1 was a 6-month, double-blind, placebo-controlled, parallel study comparing fixed doses of galantamine 12 mg bid or 16 mg bid with placebo with 653 patients randomized. The study consisted of 4 weeks screening period, 4 weeks titration period, and 5 months fixed dose period. Visits took place at the following times:

- Visit 1: Screening period: 4 weeks prior to their visit 2
- Visit 2: Start of Week 1 (baseline visit), start of double-blind period
- Visit 3: End of Week 3
- Visits 4-8: Months 2,3,4,5 and 6

During Week 1 of titration, patients received either placebo or Gal 4 mg bid. During Week 2 of titration, patients received either placebo or Gal 8 mg bid. During Week 3 of titration, patients received either placebo or Gal 12 mg bid. During Week 4, patients in the Gal 16 mg bid group received their final dose Gal 16 mg bid.

## 2.3. Efficacy Measures

The primary efficacy characteristics were measured by the Alzheimer's Disease Assessment Scale cognitive subscale (ADAS-cog/11), and the Clinician's Interview Based Impression of Change-plus (CIBIC-plus). The primary efficacy endpoints were change from baseline in ADAS-cog/11 at Month 6, and CIBIC-plus score at Month 6. The ADAS-cog/11 was measured at visits 1, 2, 3, 5 and 8 (screening, baseline, 3 weeks, 3 months and 6 months or termination), and the CIBIC-plus was measured at visits 2, 5 and 8 (baseline, 3 months and 6 months or termination).

The ADAS-cog/11 was the total of 11 items ranging from 0 to 70, whose scoring system for each item is as follows: 1: Word Recall (score: 0 to 10); 2: Word Recognition memory tests (score: 0 to 12); 3: Object and Finger Naming (score: 0 to 5); 4: Commands (score: 0 to 5); 5: Constructional Praxis (score: 0 to 5); 6: Ideational Praxis (score: 0 to 5); 7: Orientation (score: 0 to 8); 8: Remembering Test Instructions (score: 0 to 5); 9: Spoken Language Ability (score: 0 to 5); 10: Comprehension of Spoken Language (score: 0 to 5); and 12: Word Finding Difficulty (score: 0 to 5).

The CIBIC-plus was a single item scale, whose score was from 1 (markedly improved relative to baseline) to 7 (markedly worse relative to baseline).

The secondary efficacy characteristics included ADAS-cog/13, ADAS-cog/10, ADAS-cog/mem, response rate on ADAS-cog/11, Activities of Daily Living: Disability Assessment for Dementia (DAD), The Psychological General Well Being Index (PGWBI), and Health/Social Care Resource Use.

## 2.4. Statistical Analysis Plan

The two primary efficacy analyses were the change from baseline in ADAS-cog/11 at month 6, and CIBIC-plus at month 6 comparing with the placebo using the traditional observed case. Both ADAS-cog/11 and CIBIC-plus needed to be significantly better to claim a positive result.

For the analysis of ADAS-cog/11 score, a two-way analysis of variance (ANOVA) model with treatment and country as factors was used to compare the three treatment groups for the change from baseline data. The interaction between treatment and country was examined first. If the interaction term turned out to be not significant at 10% level, it was not included in the final ANOVA model. Following the ANOVA, Dunnett's test was subsequently performed to account for multiple comparisons when comparing the two galantamine groups versus placebo.

For the analysis of CIBIC-plus score, the Van Elteren test controlling for country was used for the between-treatment group comparison. The Holm's procedure was applied for the two comparisons between the galantamine doses and placebo. This procedure evaluated the p-values of the two comparisons subsequently. It ordered the two p-values. The smaller one was evaluated first. If it was found significant at 2.5% level, then the procedure continued. The comparison with the larger p-value was tested at 5% level.

## 2.5. Patient Population

### 2.5.1. Demographic

The study included male/female with AD. This also included patients living in residential homes for the elderly and day patients with dementia of the Alzheimer's type. The diagnosis was established in accordance with the NINCDS-ADRDA classification for probable Alzheimer's disease: Mild/moderate dementia as evidenced by a Mini-Mental State Examination score (MMSE) ranging from 11-24 extremes included at screening, and an Alzheimer's Disease Assessment Scale cognitive portion (ADAS-cog) score of at least 12 at screening.

Table 2.5.1 presents the demographic configuration of the study.

**Table 2.5.1 Demographic and Baseline Configuration (ITT)**

| Parameter | Placebo | GAL 12 mg bid | GAL 16 mg bid | Total |
|---|---|---|---|---|
| number of patients | 215 | 220 | 218 | 653 |
| sex | | | | |
| - Male, n (%) | 83 (38.6%) | 81 (36.8%) | 80 (36.7%) | 244 (37.4%) |
| - Female, n (%) | 132 (61.4%) | 139 (63.2%) | 138 (63.3%) | 409 (62.6%) |

| | | | | |
|---|---|---|---|---|
| race: n (%) | | | | |
| - white | 212 (99.5%) | 217 (99.5%) | 215 (99.1%) | 644 (99.4%) |
| - black | 0 | 0 | 2 (0.9%) | 2 (0.3%) |
| - other | 1 (0.5%) | 1 (0.5%) | 0 | 2 (0.3%) |
| age (years, mean±se) | 72.7 ± 0.52 | 71.9 ± 0.56 | 72.1 ± 0.58 | 72.2 ± 0.32 |
| weight (kg, mean±se) | 67.2 ± 0.83 | 66.7 ± 0.86 | 66.2 ± 0.91 | 66.7 ± 0.5 |
| smoker: n (%) | 22 (10.2%) | 20 (9.1%) | 19 (8.7%) | 61 (9.3%) |
| age at onset of cognitive problems | 69.7 ± 0.55 | 68.8 ± 0.6 | 68.9 ± 0.61 | 69.1 ± 0.34 |
| years since cognitive problem diagnosis | 3.5 ± 0.16 | 3.6 ± 0.18 | 3.7 ± 0.15 | 3.6 ± 0.1 |
| age at diagnosis of probable AD | 72.4 ± 0.51 | 71.5 ± 0.57 | 71.8 ± 0.58 | 71.9 ± 0.32 |
| years since diagnosis of AD | 0.8 ± 0.07 | 0.9 ± 0.08 | 0.8 ± 0.07 | 0.8 ± 0.04 |
| total MMSE score (mean±se) | 19.3 ± 0.24 | 19.5 ± 0.23 | 19.0 ± 0.26 | 19.3 ± 0.14 |
| ADAS-cog/11 score (mean±se) | 24.7 ± 0.64 | 25.4 ± 0.64 | 26.2 ± 0.72 | 25.4 ± 0.39 |

## 2.5.2. Patient Disposition

Table 2.5.2 presents the patients disposition.

**Table 2.5.2 Patients Disposition**

| Patient group<br>Reason for discontinuation | Placebo | GAL 12 mg bid | GAL 16 mg bid |
|---|---|---|---|
| Randomized | 215 | 220 | 218 |
| Discontinued (total) | 29 (13.5%) | 44 (20%) | 55 (25.2%) |
| Discontinued in first 4 weeks | 6 (2.8%) | 21 (9.5%) | 29 (13.3%) |
| Discontinued after 4 weeks | 23 (10.7%) | 23 (10.5%) | 26 (11.9%) |
| Reasons for discontinuation: | | | |
| - adverse events | 19 (8.8%) | 31 (14.1%) | 48 (22%) |
| - other reasons | 3 (1.4%) | 8 (3.6%) | 4 (1.8%) |
| - non-compliance | 4 (1.9%) | 4 (1.8%) | 1 (0.5%) |
| - insufficient response | 3 (1.4%) | 1 (0.5%) | 0 |
| - ineligibility to continue | 0 | 0 | 2 (0.9%) |

## 2.6. Sponsor's Analyses

All 653 patients were treated with at least one dose of trial medication but six patients had no post-baseline efficacy data (three under placebo, two under Gal 12 mg bid and one under 16 mg bid). Furthermore, three patients were given the wrong medication during the course of the trial: two placebo patients received Gal 16 mg bid and one Gal 16 mg patient received Gal 12 mg bid. The switch in medication happened at month 3. No per protocol analysis was performed because of the

small number of protocol deviations.

## 2.6.1. Sponsor's Analyses on ADAS-cog

ADAS-cog/11 ranges from 0 to 70, with the higher score indicating worse cognitive condition. The ADAS-cog/11 score could be calculated only when all 11 items were available.

The primary analysis was the observed case at month 6 on change from baseline of ADAS-cog/11 score. There were 171, 156, and 152 patients at month 6 in placebo, Gal 12 mg bid, and Gal 16 mg bid groups, respectively. The mean and mean change are presented in Table 2.6.1.1.

**Table 2.6.1.1 ADAS-cog/11: Observed Case**

| | Placebo | | | Gal 12 mg bid | | | Gal 16 mg bid | | |
|---|---|---|---|---|---|---|---|---|---|
| Time Point | n | Mean ± SE | Mean Change ± SE | n | Mean ± SE | Mean Change ± SE | n | Mean ± SE | Mean Change ± SE |
| Baseline | 211 | 24.7 ± 0.64 | | 212 | 25.4 ± 0.64 | | 212 | 26.2 ± 0.72 | |
| Month 6 | 171 | 26.7 ± 0.83 | 2.4 ± 0.44 | 156 | 24.0 ± 0.74 | -0.7 ± 0.48 | 152 | 24.6 ± 0.86 | -1.7 ± 0.47 |

For OC analysis, the ANOVA model with terms for treatment and country gave p-value .0001. The Dunnett tests gave p-values .001 for comparing Gal 12 mg bid with placebo, and .001 for comparing Gal 16 mg bid with placebo.

For LOCF analysis, the ANOVA model with terms for treatment and country gave p-value .001. The Dunnett tests gave p-values .001 for comparing Gal 12 mg bid with placebo, and .001 for comparing Gal 16 mg bid with placebo. The mean and mean change are presented in Table 2.6.1.2.

**Table 2.6.1.2 ADAS-cog/11: LOCF Case**

| | Placebo | | | Gal 12 mg bid | | | Gal 16 mg bid | | |
|---|---|---|---|---|---|---|---|---|---|
| Time Point | n | Mean ± SE | Mean Change ± SE | n | Mean ± SE | Mean Change ± SE | n | Mean ± SE | Mean Change ± SE |
| Month 6 | 207 | 27.0 ± 0.78 | 2.2 ± 0.40 | 201 | 24.8 ± 0.69 | -0.6 ± 0.40 | 205 | 24.9 ± 0.73 | -1.3 ± 0.38 |

## 2.6.2. Sponsor's Analyses on CIBIC-plus

The primary analysis was the observed case at month 6 of CIBIC-plus score. There were 174, 161,

and 155 patients at month 6 in placebo, Gal 12 mg bid, and Gal 16 mg bid groups, respectively. There were 0 in markedly improved in all three treatment groups; 1 (0.6%), 6 (3.7%), and 8 (5.2%) in moderately improved in placebo, Gal 12 mg bid, and Gal 16 mg bid groups, respectively; 29 (16.7%), 27 (16.8%), and 35 (22.6%) in minimally improved in placebo, Gal 12 mg bid, and Gal 16 mg bid groups, respectively; 56 (32.2%), 75 (46.6%), and 63 (40.6%) in no change placebo, Gal 12 mg bid, and Gal 16 mg bid groups, respectively; 58 (33.3%), 43 (26.7%), and 41 (26.5%) in minimally worsened in placebo, Gal 12 mg bid, and Gal 16 mg bid groups, respectively; 28 (16.1%), 7 (4.3%), and 8 (5.2%) in moderately worsened in placebo, Gal 12 mg bid, and Gal 16 mg bid groups, respectively; and 2 (1.1%), 3 (1.9%), and 0 in markedly worsened in placebo, Gal 12 mg bid, and Gal 16 mg bid groups, respectively.

For OC analysis, the Van Elteren test controlling for country gave p-value .001. The pairwise comparisons gave p-values .002 between Gal 12 mg bid and placebo, and .001 between Gal 16 mg bid and placebo.

For LOCF analysis, there were 199, 191, and 183 patients in placebo, Gal 12 mg bid, and Gal 16 mg bid groups, respectively. The Van Elteren test controlling for country gave p-value .001. The pairwise comparisons gave p-values .015 between Gal 12 mg bid and placebo, and .001 between Gal 16 mg bid and placebo.

## 2.6.3. Sponsor's Analyses on Subgroups

The sponsor performed subgroup analyses based on sex, age, weight, baseline ADAS-cog/11, baseline MMSE, and so on. Table 2.6.3.1 and Table 2.6.3.2 present the analyses on sex, race, and age for ADAS-cog/11, and ClBIC-plus, respectively.

**Table 2.6.3.1 ADAS-cog/11 Subgroup Analyses at Month 6**

| Subgroup | Placebo | | | Gal 12 mg bid | | | Gal 16 mg bid | | |
|---|---|---|---|---|---|---|---|---|---|
| | n | Mean | Mean Change | n | Mean | Mean Change | n | Mean | Mean Change |
| Female | 103 | 27.3 | 2.4 | 88 | 25.0 | -0.2 | 93 | 25.0 | -2.1 |
| Male | 68 | 25.7 | 3.0 | 68 | 22.6 | -1.4 | 59 | 24.0 | -1.1 |
| White | 169 | 26.7 | 2.3 | 154 | 23.9 | -0.7 | 149 | 24.7 | -1.7 |
| Non-white | 1 | 22.0 | 0.0 | 1 | 27.0 | 0.0 | 2 | 19.0 | -0.5 |
| Age<65 years | 28 | 26.1 | 3.0 | 34 | 21.3 | -2.0 | 33 | 25.9 | 0.2 |
| Age 65-85 years | 140 | 27.0 | 2.3 | 118 | 24.9 | -0.2 | 112 | 24.4 | -2.2 |
| Age>85 years | 3 | 18.3 | 1.3 | 4 | 17.8 | -3.3 | 7 | 22.7 | -2.9 |

**Table 2.6.3.2 CIBIC-plus Subgroup Analyses at Month 6**

| Subgroup | Placebo | | Gal 12 mg bid | | Gal 16 mg bid | |
|---|---|---|---|---|---|---|
| | n | Improved or no change | n | Improved or no change | n | Improved or no change |
| Female | 107 | 50 (46.7%) | 94 | 62 (66.0%) | 92 | 66 (71.7%) |
| Male | 67 | 36 (53.7%) | 67 | 46 (68.7%) | 63 | 40 (63.5%) |
| White | 173 | 86 (49.7%) | 159 | 107 (67.3%) | 152 | 104 (68.4%) |
| Non-white | 1 | 0 | 1 | 0 | 2 | 1 (50%) |
| Age<65 years | 30 | 15 (50%) | 34 | 17 (50%) | 35 | 23 (65.7%) |
| Age 65-85 years | 141 | 71 (50.4%) | 124 | 89 (71.8%) | 116 | 79 (68.1%) |
| Age>85 years | 3 | 0 | 3 | 2 (66.7%) | 4 | 4 (100%) |

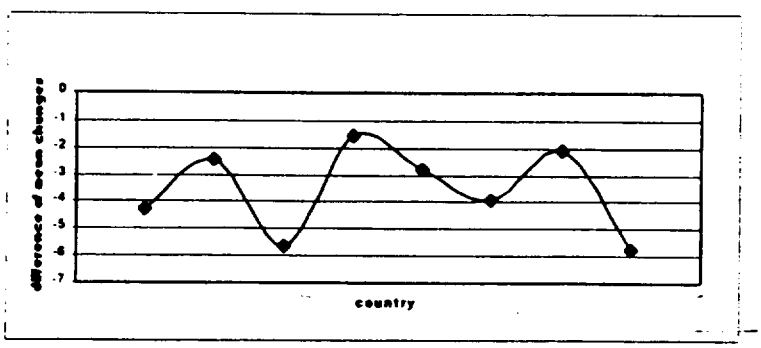
## 2.7. Reviewer's Analyses

### 2.7.1. Reviewer's Analyses on ADAS-cog

For OC analysis, this reviewer verified the sponsor's analysis, i.e., the ANOVA model with terms for treatment and country gives p-value .0001. The Dunnett tests give p-values .001 for comparing Gal 12 mg bid with placebo, and .001 for comparing Gal 16 mg bid with placebo.

Among 8 countries, 7 of 8 show that Gal 12 mg bid is numerically superior to placebo except Germany, and 7 of 8 show that Gal 16 mg bid is numerically superior to placebo except Norway. Figure 2.7.1 presents the difference of mean changes by country between Gal (combining Gal 12 mg bid and Gal 16 mg bid together) and placebo. A negative value indicates that Gal is numerically superiority to placebo.

**Figure 2.7.1 ADAS-cog: Difference of Mean Changes by Country**




For LOCF analysis, this reviewer verified the sponsor's analysis, i.e., the ANOVA model with terms for treatment and country gives p-value .001. The Dunnett tests give p-values .001 for comparing Gal 12 mg bid with placebo, and .001 for comparing Gal 16 mg bid with placebo.

Table 2.7.1 presents the dropouts for placebo and Gal (combining Gal 8 mg bid and 16 mg bid together) at Month 3 and Month 6. There is no bias shown in the dropouts.

**Table 2.7.1 ADAS-cog/11: Dropouts**

| Dropout at | Dropout number | Baseline Mean ± SD | Week 3 Mean ± SD | Month 3 Mean ± SD |
|---|---|---|---|---|
| Month 3 | Gal 66<br>Pla 13 | 26.3 ± 9.7<br>30.0 ± 13.4 | 25.6± 9.9<br>30.9± 12.7 | |
| Month 6 | Gal 31<br>Pla 21 | 27.9 ± 12.1<br>24.5 ± 11.2 | 25.8± 12.3<br>25.0 ± 11.0 | 26.0 ± 11.9<br>25.0 ± 13.4 |

## 2.7.2. Reviewer's Analyses on CIBIC-plus

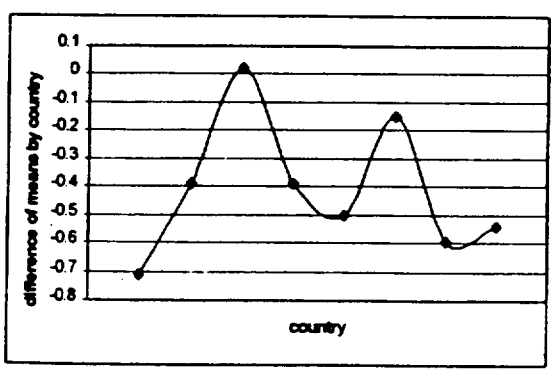
For OC analysis, this reviewer verified the sponsor's analysis, i.e., the Van Elteren test controlling for country gives p-value .001. The pairwise comparisons give p-values .002 between Gal 12 mg bid and placebo, and .001 between Gal 16 mg bid and placebo. The mean ± SD at month 6 for CIBIC-plus are presented in Table 2.7.2.1.

**Table 2.7.2.1 CIBIC-plus: Observed Case**

| | Placebo | | Gal 12 mg bid | | Gal 16 mg bid | |
|---|---|---|---|---|---|---|
| Time Point | n | Mean ± SD | n | Mean ± SD | n | Mean ± SD |
| Month 6 | 174 | 4.51 ± 1.01 | 161 | 4.17 ± 0.95 | 155 | 4.04 ± 0.95 |

Among 8 countries, 6 of 8 show that Gal 12 mg bid are numerically superior to placebo, and 8 of 8 show that Gal 16 mg bid are numerically superior to placebo. Figure 2.7.2 presents the difference of mean changes by country between Gal (combining Gal 12 mg bid and Gal 16 mg bid together) and placebo. A negative value indicates that Gal is numerically superior to placebo.

**Figure 2.7.2 CIBIC-plus: Difference of Mean Changes by Country**



For LOCF analysis, this reviewer verified the sponsor's analysis, i.e., theVan Elteren test controlling for country gives p-value .001. The pairwise comparisons give p-values .015 between Gal 12 mg bid and placebo, and .001 between Gal 16 mg bid and placebo. The mean ± SD at month 6 for CIBIC-plus are presented in Table 2.7.2.2.

**Table 2.7.2.2 CIBIC-plus: LOCF Case**

| | Placebo | | Gal 12 mg bid | | Gal 16 mg bid | |
|---|---|---|---|---|---|---|
| Time Point | n | Mean ± SD | n | Mean ± SD | n | Mean ± SD |
| Month 6 | 199 | 4.48 ± 0.97 | 191 | 4.22 ± 0.96 | 183 | 4.05 ± 0.97 |

### 2.7.3. Reviewer's Analyses on Subgroups

This reviewer verified the sponsor's analysis. See details in Section 2.6.3.

## 3. GAL-USA-1

### 3.1. Objective

The primary objective was to assess the efficacy, safety and tolerability of galantamine 12 mg bid or 16 mg bid compared with placebo in patients with Alzheimer's disease with mild to moderate symptoms.

### 3.2. Study Design

GAL-USA-1 is a 6-month, double-blind, placebo-controlled, parallel study comparing fixed doses of galantamine 12 mg bid or 16 mg bid with placebo with 653 patients randomized. The study consisted of 4 weeks screening period, 4 weeks titration period, and 5 months fixed dose period. Visits took place at the following times:

- Visit 1: Screening period: 4 weeks prior to their visit 2
- Visit 2: Start of Week 1 (baseline visit), start of double-blind period
- Visit 3: End of Week 3
- Visits 4-8: Months 2,3,4,5 and 6

During Week 1 of titration, patients received either placebo or Gal 4 mg bid. During Week 2 of titration, patients received either placebo or Gal 8 mg bid. During Week 3 of titration, patients received either placebo or Gal 12 mg bid. During Week 4, the patients in the Gal 16 mg bid group received their final dose Gal 16 mg bid.

## 3.3. Efficacy Measures

The primary efficacy characteristics were measured by the Alzheimer's Disease Assessment Scale cognitive subscale (ADAS-cog/11), and the Clinician's Interview Based Impression of Change-plus (CIBIC-plus). The primary efficacy endpoints were change from baseline in ADAS-cog/11 at Month 6, and CIBIC-plus score at Month 6. The ADAS-cog/11 was measured at visits 1, 2, 3, 5 and 8 (screening, baseline, 3 weeks, 3 months and 6 months or termination), and the CIBIC-plus was measured at visits 2, 5 and 8 (baseline, 3 months and 6 months or termination).

The secondary efficacy characteristics included ADAS-cog/13, ADAS-cog/10, ADAS-cog/mem, response rate on ADAS-cog/11, Activities of Daily Living: Disability Assessment for Dementia (DAD), The Psychological General Well Being Index (PGWBI), and Health/Social Care Resource Use.

## 3.4. Statistical Analysis Plan

The two primary efficacy analyses were the change from baseline in ADAS-cog/11 at month 6, and CIBIC-plus score at month 6, comparing with the placebo using the traditional observed case. Both ADAS-cog/11 and CIBIC-plus needed to be significantly better to claim a positive result.

For the analysis of ADAS-cog/11 score, a two-way analysis of variance (ANOVA) model with treatment and investigator as factors was used to compare the three treatment groups for the change from baseline data. The interaction between treatment and investigator was examined first. If the interaction term turned out to be not significant at 10% level, it was not included in the final ANOVA model. Following the ANOVA, Dunnett's test was subsequently performed to account for multiple comparisons when comparing the two galantamine groups versus placebo.

For the analysis of CIBIC-plus score, the Van Elteren test controlling for investigator was used for the between-treatment group comparison. The Holm's procedure was applied for the two comparisons between the galantamine doses and placebo. This procedure evaluated the p-values of the two comparisons subsequently. It ordered the two p-values. The smaller one was evaluated first. If it was found significant at 2.5% level, then the procedure continued. The comparison with the larger p-value was tested at 5% level.

## 3.5. Patient Population

### 3.5.1. Demographic

The study included male/female with AD. The diagnosis was established in accordance with the NINCDS-ADRDA classification for probable Alzheimer's disease: Mild/moderate dementia as evidenced by a Mini-Mental State Examination score (MMSE) ranging from 11-24, boundaries

included at screening, and an Alzheimer's Disease Assessment Scale cognitive portion (ADAS-cog) score of at least 12 at screening.

Table 3.5.1 presents the demographic configuration of the study.

**Table 3.5.1 Demographic and Baseline Configuration (ITT)**

| Parameter | Placebo | GAL 12 mg bid | GAL 16 mg bid | Total |
|---|---|---|---|---|
| number of patients | 213 | 212 | 211 | 636 |
| sex | | | | |
| - Male, n (%) | 82 (38.5%) | 73 (34.4%) | 87 (41.2%) | 242 (38.1%) |
| - Female, n (%) | 131 (61.5%) | 139 (65.6%) | 124 (58.8%) | 394 (61.9%) |
| race: n (%) | | | | |
| - white | 196 (92%) | 195 (92%) | 190 (90%) | 581 (91.4%) |
| - black | 11 (5.2%) | 11 (5.2%) | 8 (3.8%) | 30 (4.7%) |
| - hispanic | 4 (1.9%) | 5 (2.4%) | 12 (5.7%) | 21 (3.3%) |
| - oriental | 0 | 1 (0.5%) | 0 | 1 (0.2%) |
| - other | 2 (0.9%) | 0 | 1 (0.5%) | 3 (0.5%) |
| age (years, mean±se) | 75.3 ± 0.58 | 75.9 ± 0.51 | 75.0 ± 0.58 | 75.4 ± 0.32 |
| weight (kg, mean±se) | 67.08 ± 0.97 | 67.54 ± 1.01 | 67.34 ± 1.00 | 67.32 ± 0.57 |
| smoker: n (%) | 11 (5.2%) | 16 (7.5%) | 17 (8.1%) | 44 (6.9%) |
| age at onset of cognitive problems | 71.5 ± 0.65 | 72.5 ± 0.55 | 71.4 ± 0.60 | 71.8 ± 0.35 |
| years since cognitive problem diagnosis | 4.34± 0.20 | 3.8 ± 0.18 | 4.13 ± 0.18 | 4.09 ± 0.11 |
| age at diagnosis of probable AD | 74.7 ± 0.59 | 75.3 ± 0.53 | 74.1 ± 0.59 | 74.7 ± 0.33 |
| years since diagnosis of AD | 1.13 ± 0.105 | 1.02 ± 0.102 | 1.45 ± 0.125 | 1.2 ± 0.064 |
| total MMSE score (mean±se) | 19.2 ± 0.27 | 19.5 ± 0.27 | 19.1 ± 0.29 | 19.3 ± 0.16 |
| ADAS-cog/11 score (mean±se) | 25.7 ± 0.78 | 24.8 ± 0.67 | 25.8 ± 0.83 | 25.4 ± 0.44 |

## 3.5.2. Patient Disposition

As Table 3.5.2 presents the patients disposition.

**Table 3.5.2 Patients Disposition**

| Patient group<br>Reason for discontinuation | Placebo | GAL 12 mg bid | GAL 16 mg bid |
|---|---|---|---|
| Randomized | 213 | 212 | 211 |
| Discontinued (total) | 41 (19.2%) | 68 (32.1%) | 89 (42.2%) |
| Discontinued in first 4 weeks | 6 (2.8%) | 22 (10.4%) | 35 (16.6%) |

| | | | |
|---|---|---|---|
| Discontinued after 4 weeks | 35 (16.9%) | 46 (24.4%) | 54 (30.7%) |
| Reasons for discontinuation: | | | |
| - adverse events | 16 (7.5%) | 49 (23.1%) | 67 (31.8%) |
| - other reasons | 3 (1.4%) | 3 (1.4%) | 4 (1.9%) |
| - non-compliance | 2 (0.9%) | 3 (1.4%) | 4 (1.9%) |
| - patient withdrew consent | 19 (8.9%) | 1 1(5.2%) | 13 (6.2%) |
| - patient lost to follow up | 1 (0.5%) | 2 (0.9%) | 1 (0.5%) |

## 3.6. Sponsor's Analyses

All 636 randomized patients were treated with at least one dose of trial medication, and no patients were assigned to an incorrect treatment group.

The sponsor reported that one investigator was found to have provided unreliable data in a trial (GAL-USA-10) that was ongoing after the finalization of the report for GAL-USA-1. This investigator had participated as a for this GAL-USA-1 trial. This sub-investigator, was only involved in the CIBIC-plus assessment for site. A re-analysis was performed by the sponsor excluding site from the two primary efficacy endpoints. The results of the re-analysis had no impact on the original conclusions.

### 3.6.1. Sponsor's Analyses on ADAS-cog

Among 636 patients, 7 patients did not have baseline ADAS-cog/11 scores: 6 patients had one or more item scores missing and 1 patient had an invalid baseline measurement that was taken 3 days after the patient started the medication.

The primary analysis was the observed case at month 6 on change from baseline of ADAS-cog/11 score. There were 157, 131, and 117 patients at month 6 in placebo, Gal 12 mg bid, and Gal 16 mg bid groups, respectively. The mean and mean change are presented in Table 3.6.1.1.

**Table 3.6.1.1 ADAS-cog/11: Observed Case**

| | Placebo | | | Gal 12 mg bid | | | Gal 16 mg bid | | |
|---|---|---|---|---|---|---|---|---|---|
| Time Point | n | Mean ± SE | Mean Change ± SE | n | Mean ± SE | Mean Change ± SE | n | Mean ± SE | Mean Change ± SE |
| Baseline | 213 | 25.7 ± 0.78 | | 207 | 24.8 ± 0.67 | | 209 | 25.8 ± 0.83 | |
| Month 6 | 157 | 26.7 ± 1.13 | 2.2 ± 0.52 | 131 | 22.4 ± 0.85 | -1.7 ± 0.45 | 117 | 23.9 ± 1.08 | -1.6 ± 0.66 |

The ANOVA model with terms for treatment and center gave p-value .0001, where centers (9, 28,

30), (20, 32), (21, 33), (3, 29), (11, 31), and (10, 12, 18) were pooled together, respectively. The Dunnett tests gave p-values .001 for comparing Gal 12 mg bid with placebo, and .001 for comparing Gal 16 mg bid with placebo.

For LOCF analysis, the ANOVA model with terms for treatment and center gave p-value .001, where centers (9, 28, 30), (20, 32), (21, 33), (3, 29), (11, 31), and (10, 12, 18) were pooled together, respectively. The Dunnett tests gave p-values .001 for comparing Gal 12 mg bid with placebo, and .001 for comparing Gal 16 mg bid with placebo.

**Table 3.6.1.2 ADAS-cog/11: LOCF Case**

| | Placebo | | | Gal 12 mg bid | | | Gal 16 mg bid | | |
|---|---|---|---|---|---|---|---|---|---|
| Time Point | n | Mean ± SE | Mean Change ± SE | n | Mean ± SE | Mean Change ± SE | n | Mean ± SE | Mean Change ± SE |
| Month 6 | 207 | 27.6 ± 0.98 | 2.0 ± 0.45 | 202 | 23.0 ± 0.71 | -1.9 ± 0.36 | 197 | 24.3 ± 0.84 | -1.4 ± 0.44 |

## 3.6.2. Sponsor's Analyses on CIBIC-plus

The primary analysis was the observed case at month 6 of CIBIC-plus score. There were 159, 135, and 118 patients at month 6 in placebo, Gal 12 mg bid, and Gal 16 mg bid groups, respectively. There were 0, 1 (0.7%), and 2 (1.7%) in markedly improved in placebo, Gal 12 mg bid, and Gal 16 mg bid groups, respectively; 7 (4.4%), 4 (3.0%), and 4 (3.4%) in moderately improved in placebo, Gal 12 mg bid, and Gal 16 mg bid groups, respectively; 14 (8.8%), 22 (16.3%), and 17 (14.4%) in minimally improved in placebo, Gal 12 mg bid, and Gal 16 mg bid groups, respectively; 67 (42.1%), 68 (50.4%), and 57 (48.3%) in no change placebo, Gal 12 mg bid, and Gal 16 mg bid groups, respectively; 47 (29.6%), 29 (21.5%), and 30 (25.4%) in minimally worsened in placebo, Gal 12 mg bid, and Gal 16 mg bid groups, respectively; 23 (14.5%), 8 (5.9%), and 7 (5.9%) in moderately worsened in placebo, Gal 12 mg bid, and Gal 16 mg bid groups, respectively; and 1 (0.6%), 3 (2.2%), and 1 (0.8%) in markedly worsened in placebo, Gal 12 mg bid, and Gal 16 mg bid groups, respectively.

For OC analysis, the Van Elteren test controlling for center gave p-value .05. The pairwise comparisons gave p-values .05 between Gal 12 mg bid and placebo, and .05 between Gal 16 mg bid and placebo.

For LOCF analysis, there were 196, 186, and 171 patients in placebo, Gal 12 mg bid, and Gal 16 mg bid groups, respectively. The Van Elteren test controlling for center gave p-value .007. The pairwise comparisons gave p-values .003 between Gal 12 mg bid and placebo, and .021 between Gal 16 mg bid and placebo.

### 3.6.3. Sponsor's Analyses on Subgroups

The sponsor performed subgroup analyses based on sex, age, weight, baseline ADAS-cog/11, baseline MMSE, and so on. Table 3.6.3.1 and Table 3.6.3.2 present the analyses on sex, race, and age for ADAS-cog/11, and CIBIC-plus, respectively.

**Table 3.6.3.1 ADAS-cog/11 Subgroup Analyses at Month 6**

| Subgroup | Placebo | | | Gal 12 mg bid | | | Gal 16 mg bid | | |
|---|---|---|---|---|---|---|---|---|---|
| | n | Mean | Mean Change | n | Mean | Mean Change | n | Mean | Mean Change |
| Female | 97 | 28.7 | 2.4 | 77 | 22.7 | -1.8 | 56 | 27.1 | -0.9 |
| Male | 60 | 23.4 | 1.7 | 54 | 22.0 | -1.5 | 61 | 20.9 | -2.2 |
| White | 146 | 27.0 | 2.4 | 121 | 21.9 | -1.8 | 110 | 24.3 | -1.6 |
| Non-white | 11 | 22.1 | -1.7 | 10 | 29.3 | -0.5 | 7 | 17.4 | -1.0 |
| Age<65 years | 17 | 16.8 | 0.2 | 9 | 21.4 | -0.8 | 14 | 18.4 | 0.2 |
| Age 65-85 years | 131 | 27.8 | 2.3 | 115 | 22.5 | -1.7 | 96 | 24.3 | -2.1 |
| Age>85 years | 9 | 28.8 | 3.8 | 7 | 23.1 | -3.4 | 7 | 29.1 | 2.9 |

**Table 3.6.3.2 CIBIC-plus Subgroup Analyses at Month 6**

| Subgroup | Placebo | | Gal 12 mg bid | | Gal 16 mg bid | |
|---|---|---|---|---|---|---|
| | n | Improved or no change | n | Improved or no change | n | Improved or no change |
| Female | 100 | 53 (53.0%) | 81 | 54 (66.7%) | 57 | 38 (66.7%) |
| Male | 59 | 35 (59.3%) | 54 | 41 (75.9%) | 61 | 42 (68.9%) |
| White | 148 | 83 (56.1%) | 126 | 91 (72.2%) | 111 | 74 (66.7%) |
| Non-white | 11 | 5 (45.5%) | 9 | 4 (44.4%) | 7 | 6 (85.7%) |
| Age<65 years | 18 | 12 (66.7%) | 12 | 9 (70%) | 17 | 14 (78.6%) |
| Age 65-85 years | 132 | 69 (52.3%) | 118 | 83 (70.3%) | 97 | 65 (67%) |
| Age>85 years | 9 | 7 (77.8%) | 7 | 5 (71.4%) | 7 | 4 (57.1%) |

## 3.7. Reviewer's Analyses

### 3.7.1. Reviewer's Analyses on ADAS-cog

For OC analysis, this reviewer verified the sponsor's analysis, i.e., the ANOVA model with terms for treatment and center gives p-value .0001. The Dunnett tests give p-values .001 for comparing Gal 12 mg bid with placebo, and .001 for comparing Gal 16 mg bid with placebo.

Figure 3.7.1 presents the difference of mean changes between Gal (combining Gal 12 mg bid and 16 mg bid together) and placebo. A negative value indicates that Gal is numerically superior to

placebo. Among 33 centers, 27 of 33 show that Gal is numerically superior to placebo. The difference of mean changes of Center 9 was larger, which had only 3 patients with 1 patient in each arm. The changes were -12, -2, and 9 for placebo, Gal 12 mg bid, and Gal 16 mg bid, respectively.

**Figure 3.7.1 ADAS-cog: Difference of Mean Changes by Center**

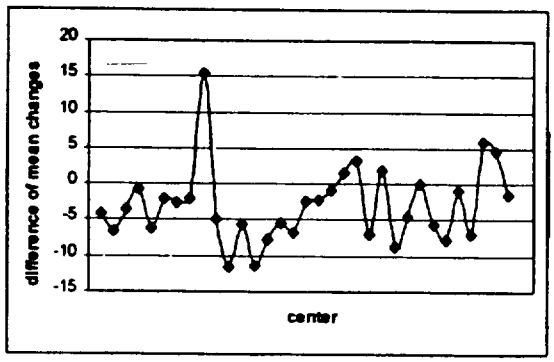



Table 3.7.1.1 presents the data from site.

**Table 3.7.1.1 ADAS-cog/11: Observed Case ( Site)**

| | Placebo | | | Gal 12 mg bid | | | Gal 16 mg bid | | |
|---|---|---|---|---|---|---|---|---|---|
| Time Point | n | Mean ± SD | Mean Change ± SD | n | Mean ± SD | Mean Change ± SD | n | Mean ± SD | Mean Change ± SD |
| Baseline | 3 | 24.33 ± 17.62 | | 2 | 23.5 ± 12.02 | | 4 | 38.00 ± 13.09 | |
| Month 6 | 2 | 18.00 ± 8.49 | -1.0 ± 12.73 | 1 | 14.00 ± | -1.0 ± | 1 | 25.00 ± | -15.00 ± |

After excluding data from site, there are 155, 130, and 116 patients at month 6 in placebo, Gal 12 mg bid, and Gal 16 mg bid groups, respectively. The mean change ± SD at month 6 are 2.2 ± 6.48, -1.7 ± 5.21, and -1.4 ± 7.02 for placebo, Gal 12 mg bid, and Gal 16 mg bid groups, respectively. The ANOVA model with terms for treatment and center gives p-value .0001, where centers with few patients are pooled together as the sponsor did. The Dunnett tests give p-values .001 for comparing Gal 12 mg bid with placebo, and .001 for comparing Gal 16 mg bid with placebo.

For LOCF analysis, this reviewer verified the sponsor's analysis, i.e., the ANOVA model with terms for treatment and center gives p-value .001. The Dunnett tests give p-values .001 for comparing Gal 12 mg bid with placebo, and .001 for comparing Gal 16 mg bid with placebo. After excluding data from site, there are 204, 200, and 193 patients at month 6 in placebo, Gal 12 mg bid, and Gal 16 mg bid groups, respectively. The mean change ± SD at month 6 are 2.0 ± 6.39, -1.9 ±

5.06, and -1.3 ± 6.18 for placebo, Gal 12 mg bid, and Gal 16 mg bid groups, respectively. The ANOVA model with terms for treatment and center gives p-value .0001. The Dunnett tests give p-values .001 for comparing Gal 12 mg bid with placebo, and .001 for comparing Gal 16 mg bid with placebo.

Table 3.7.1.2 presents the dropouts for placebo and Gal (combining Gal 8 mg bid and 16 mg bid together) at Month 3 and Month 6. There is no bias shown in the dropouts.

**Table 3.7.1.2 ADAS-cog/11: Dropouts**

| Dropout at | Dropout number | Baseline Mean ± SD | Week 3 Mean ± SD | Month 3 Mean ± SD |
|---|---|---|---|---|
| Month 3 | Gal 108 | 25.0 ± 11.3 | 23.7± 11.0 | |
| | Pla 17 | 28.0 ± 11.3 | 26.5± 11.9 | |
| Month 6 | Gal 43 | 29.1 ± 11.0 | 26.8± 10.4 | 26.9 ± 11.0 |
| | Pla 30 | 29.8 ± 13.1 | 30.0 ± 11.9 | 32.6 ± 15.1 |

## 3.7.2. Reviewer's Analyses on CIBIC-plus

In the sponsor's OC analysis, there were 159, 135, and 118 patients at month 6 in placebo, Gal 12 mg bid, and Gal 16 mg bid groups, respectively. This reviewer only has 134 in Gal 12 mg bid group. This reviewer thought that the sponsor included the patient A35521 in their analysis, who was not marked as ITT in the data set. Using 134 in Gal 12 mg bid group, the mean ± SD at month 6 for CIBIC-plus are presented in Table 3.7.2.1.

**Table 3.7.2.1 CIBIC-plus: Observed Case**

| | Placebo | | Gal 12 mg bid | | Gal 16 mg bid | |
|---|---|---|---|---|---|---|
| Time Point | n | Mean ± SD | n | Mean ± SD | n | Mean ± SD |
| Month 6 | 159 | 4.43 ± 1.01 | 134 | 4.15 ± 0.99 | 118 | 4.14 ± 0.99 |

The Van Elteren test controlling for center gives p-value .026. The pairwise comparisons give p-values .019 between Gal 12 mg bid and placebo, and .017 between Gal 16 mg bid and placebo.

Table 3.7.2.2 presents data from site.

**Table 3.7.2.2 CIBIC-plus: Observed Case (**

| | Placebo | Gal 12 mg bid | Gal 16 mg bid |
|---|---|---|---|

| Time Point | n | Mean ± SD | n | Mean ± SD | n | Mean ± SD |
|---|---|---|---|---|---|---|
| Month 6 | 2 | 5.0 ± 1.41 | 3 | 5.0 ± 1.73 | 1 | 4.0 ± |

After excluding data from site, there are 157, 131, and 117 patients at month 6 in placebo, Gal 12 mg bid, and Gal 16 mg bid groups, respectively. The Van Elteren test controlling for center gives p-value .029. The pairwise comparisons give p-values .019 between Gal 12 mg bid and placebo, and .021 between Gal 16 mg bid and placebo.

In the sponsor's LOCF analysis, there were 196, 186, and 171 patients in placebo, Gal 12 mg bid, and Gal 16 mg bid groups, respectively. This reviewer only has 185 patients in Gal 12 mg bid group. This reviewer thought that the sponsor included the patient A35521 in their analysis, who was not marked as ITT in the data set. Using 185 in Gal 12 mg bid group, the mean ± SD at month 6 for CIBIC-plus are presented in Table 3.7.4. The Van Elteren test controlling for center gives p-value .005. The pairwise comparisons give p-values .002 between Gal 12 mg bid and placebo, and .021 between Gal 16 mg bid and placebo.

**Table 3.7.2.3 CIBIC-plus: LOCF Case**

| | Placebo | | Gal 12 mg bid | | Gal 16 mg bid | |
|---|---|---|---|---|---|---|
| Time Point | n | Mean ± SD | n | Mean ± SD | n | Mean ± SD |
| Month 6 | 196 | 4.38 ± 0.99 | 185 | 4.10 ± 1.01 | 171 | 4.17 ± 0.90 |

For LOCF analysis, after excluding site, there are 193, 182, and 168 patients in placebo, Gal 12 mg bid, and Gal 16 mg bid groups, respectively. The mean ± SD at month 6 for CIBIC-plus are 4.38 ± 0.99, 4.08 ± 1.00, and 4.17 ± 0.91 for placebo, Gal 12 mg bid, and Gal 16 mg bid groups, respectively. The Van Elteren test controlling for center gives p-value .006. The pairwise comparisons give p-values .002 between Gal 12 mg bid and placebo, and .031 between Gal 16 mg bid and placebo.

### 3.7.3. Reviewer's Analyses on Subgroups

This reviewer verified the sponsor's analysis. This reviewer thought that the sponsor included the patient A35521 in CIBIC-plus analysis who was not marked as ITT in the data set. See details in Section 3.6.3.

## 4. GAL-USA-10

## 4.1. Objective

The primary objective was to evaluate the assess the efficacy and safety of galantamine 4 mg bid, 8 mg bid, and 12 mg bid compared with placebo when a slow-titration regimen was employed.

## 4.2. Study Design

GAL-USA-10 was a 5-month, double-blind, placebo-controlled, parallel study comparing slow-titration of galantamine 4 mg bid, 8 mg bid or 12 mg bid with placebo. Visits took place at the following times:

- Visit 1: Screening period: 4 weeks prior to their visit 2
- Visit 2: Start of Week 1 (baseline visit), start of double-blind period
- Visit 3: End of Week 4
- Visits 4-5: Weeks 13 and Month 5

All patients were included in a 1-month single-blind, placebo run-in period. At the end of the run-in period, patients were randomized to one of four treatment groups: placebo, Gal 12 mg bid (8 weeks titration to reach dose), Gal 8 mg bid (4 weeks titration to reach dose), and Gal 4 mg bid (no titration needed). During the first four weeks of treatment, patients received either placebo or Gal 4 mg bid. During Visit 3 (Week 4), the galantamine dose was increased to 8 mg bid for patients in the Gal 12 and 8 mg bid groups. The treatment in the placebo and Gal 4 mg bid groups was not changed. At Visit 4 (Week 12), the galantamine dose was increased to 12 mg bid for patients in the Gal 12 mg bid group.

## 4.3. Efficacy Measures

The primary efficacy characteristics were measured by the Alzheimer's Disease Assessment Scale cognitive subscale (ADAS-cog/11), and the Clinician's Interview Based Impression of Change-plus (CIBIC-plus). The primary efficacy endpoints were change from baseline in ADAS-cog/11 at Month 5, and CIBIC-plus score at Month 5. The ADAS-cog/11 was measured at visits 1, 2, 3, 4 and 5 (screening, baseline, Week 4, Week 13, and Month 5 or termination), and the CIBIC-plus was measured at visits 2, 3, 4 and 5 (baseline, Week 4, Week 13, and Month 5 or termination).

The secondary efficacy characteristics included ADAS-cog/13, ADAS-cog/10, ADAS-cog/mem, percentage of responders based on ADAS-cog/11, Neurophychiatric Inventory (NPI), and Alzheimer's Disease Cooperative Study ADCS/ADL Inventory.

## 4.4. Statistical Analysis Plan

The two primary efficacy analyses were the change from baseline in ADAS-cog/11 at month 5, and CIBIC-plus at month 5, comparing with the placebo using the traditional observed case. Both

ADAS-cog/11 and CIBIC-plus needed to be significantly better to claim a positive result.

For the analysis of ADAS-cog/11 score, an analysis of variance (ANOVA) model with treatment and investigator as factors was used to compare the three treatment groups for the change from baseline. The interaction between treatment and investigator was examined first. If the interaction term turned out to be not significant at 10% level, it was not included in the final ANOVA model. Following the ANOVA, a step-down closed testing procedure was used. The step-down procedure was defined a priori in a sequence of hypotheses in hierarchical order. The first hypothesis in the sequence tests the difference between the highest does Gal 12 mg bid and placebo at $\alpha$=.05. If it was rejected, then the procedure continued. The hypothesis in the sequence was again performed at 5% level, i.e., testing the difference between the second highest dose Gal 8 mg bid and placebo. The procedure stopped if lack of significance was found at the first or second step. Since it was a closed testing procedure, the step-down approach preserved the experiment-wise $\alpha$ level (i.e., 5%) and provided a multiplicity adjustment inherent with comparisons of several dose levels with placebo. There was no adjustment for comparison between each pair of galantamine doses. Treatment differences were assessed by using the means and least-squares from the ANOVA model.

For the analysis of CIBIC-plus score, the Van Elteren test controlling for investigator was used for the between-treatment group comparison. This analysis was repeated for the comparisons between each galantamine dose and placebo to assess dose-response relationship and between each pair of the galantamine doses. The step-down closed testing procedure (described in the last paragraph) was again applied in comparisons between each galantamine dose and placebo.

## 4.5. Patient Population

### 4.5.1. Demographic

The study included male/female outpatients with probable AD in accordance with the NINCDS-ADRDA classification for probable Alzheimer's disease: Mild/moderate dementia as evidenced by a Mini-Mental State Examination score (MMSE) ranging from 10-22 inclusive at screening, and an Alzheimer's Disease Assessment Scale cognitive portion (ADAS-cog) score of at least 18 at screening.

Table 4.5.1 presents the demographic configuration of the study.

**Table 4.5.1 Demographic and Baseline Configuration (ITT)**

| Parameter | Placebo | GAL 4 mg bid | GAL 8 mg bid | GAL 12 mg bid |
|---|---|---|---|---|
| number of patients | 286 | 140 | 279 | 273 |
| sex | | | | |
| - Male, n (%) | 108 (37.8%) | 50 (35.7%) | 105 (37.6%) | 90 (33.0%) |

| | | | | |
|---|---|---|---|---|
| - Female, n (%) | 178 (62.2%) | 90 (64.3%) | 174 (62.4%) | 183 (67.0%) |
| race: n (%) | | | | |
| - caucasian | 267 (93.4%) | 132 (94.3%) | 260 (93.2%) | 249 (91.2%) |
| - black | 13 (4.5%) | 5 (3.6%) | 12 (4.3%) | 14 (5.1%) |
| - hispanic | 3 (1.0%) | 3 (2.1%) | 5 (1.8%) | 4 (1.5%) |
| - oriental | 3 (1.0%) | 0 | 1 (0.4%) | 3 (1.1%) |
| - other | 0 | 0 | 1 (0.4%) | 3 (1.1%) |
| age (years, mean±se) | 77.1 ± 0.46 | 76 ± 0.61 | 76.3 ± 0.49 | 77.7 ± 0.43 |
| weight (kg, mean±se) | 67.55 ± 0.835 | 69.88 ± 1.413 | 68.12 ± 0.867 | 66.55 ± 0.803 |
| smoker: n (%) | 15 (5.2%) | 6 (4.3%) | 15 (5.4%) | 11 (4.0%) |
| age at onset of cognitive problems | 73.2 ± 0.49 | 72.3 ± 0.64 | 72.6 ± 0.5 | 74.2 ± 0.47 |
| years since cognitive problem diagnosis | 4.33± 0.152 | 4.14 ± 0.212 | 4.22 ± 0.164 | 3.92 ± 0.164 |
| age at diagnosis of probable AD | 76.1 ± 0.47 | 75.2 ± 0.63 | 75.4 ± 0.5 | 76.8 ± 0.44 |
| years since diagnosis of AD | 1.42 ± 0.104 | 1.26 ± 0.122 | 1.42 ± 0.11 | 1.32 ± 0.108 |
| total MMSE score (mean±se) | 17.7 ± 0.21 | 18 ± 0.3 | 17.8 ± 0.21 | 17.7 ± 0.23 |
| ADAS-cog/11 score (mean±se) | 29.4 ± 0.63 | 27.8 ± 0.94 | 29.4 ± 0.66 | 29.0 ± 0.67 |

## 4.5.2. Patient Disposition

Table 4.5.2 presents the patients disposition.

**Table 4.5.2 Patients Disposition**

| Patient group<br>Reason for discontinuation | Placebo | GAL 4 mg bid | GAL 8 mg bid | GAL 12 mg bid |
|---|---|---|---|---|
| Randomized | 286 | 140 | 279 | 273 |
| Any reason | 46 (16.1%) | 32 (22.9%) | 60 (21.5%) | 61 (22.3%) |
| During first 8 weeks | 22 (7.7%) | 13 (9.34%) | 27 (9.7%) | 22 (8.1%) |
| After 8 weeks | 24 (9.1%) | 19 (15.0%) | 33 (13.1%) | 39 (15.5%) |
| Adverse events | 20 (7.0%) | 9 (6.4%) | 19 (6.8%) | 27 (9.9%) |
| Inefficacy | 0 | 1 (0.7%) | 0 | 2 (0.7%) |
| Other reasons | 23 (8.0%) | 18 (12.9%) | 30 (10.8%) | 20 (7.3%) |
| Ineligible to continue trial | 0 | 0 | 4 (1.4%) | 2 (0.7%) |
| Non-compliant | 3 (1.0%) | 4 (2.9%) | 7 (2.5%) | 2 (0.7%) |

## 4.6. Sponsor's Analyses

All 979 randomized patients were randomized across the four treatment groups. One patient (A73256) was randomized to the Gal 8 mg bid group but received no trial medication. The other 978 patients entered the double-blind treatment phase.

The sponsor excluded site for the primary analysis for both ADAS-cog and CIBIC-plus. The sponsor stated that site was closed due to its lack of adherence to "Good Clinical Practices".

## 4.6.1. Sponsor's Analyses on ADAS-cog

The primary analysis was the observed case at month 5 on change from baseline of ADAS-cog/11 score. There were 225, 101, 208, and 211 patients at month 5 in placebo, Gal 4 mg bid, Gal 8 mg bid, and Gal 12 mg bid groups, respectively. The mean and mean change are presented in Table 4.6.1.1.

**Table 4.6.1.1 ADAS-cog/11: Observed Case (Excluding ' Site)**

| | Placebo | | | Gal 4 mg bid | | | Gal 8 mg bid | | | Gal 12 mg bid | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Time Point | n | Mean ± SE | Mean Change ± SE | n | Mean ± SE | Mean Change ± SE | n | Mean ± SE | Mean Change ± SE | n | Mean ± SE | Mean Change ± SE |
| Baseline | 269 | 29.4 ± 0.63 | | 132 | 27.8 ± 0.94 | | 266 | 29.4 ± 0.66 | | 262 | 29.0 ± 0.67 | |
| Month 5 | 225 | 30.3 ± 0.85 | 1.8 ± 0.43 | 101 | 27.3 ± 1.12 | 0.1 ± 0.58 | 208 | 26.9 ± 0.85 | -1.5 ± 0.40 | 211 | 26.7 ± 0.79 | -1.8 ± 0.44 |

The ANOVA model with terms for treatment and center gave p-value .001, where centers (5,15, 36, 45, 48, 53), (2, 28, 31, 40, 55), (3, 4, 7, 10, 21, 54), (8, 11), (25, 35), (19, 20, 42), (38, 43), (26, 33), (41, 49), (32, 57), and (16, 17) were pooled together, respectively. The pairwise comparisons gave p-values .037 between Gal 4 mg bid and placebo groups, .001 between Gal 8 mg bid and placebo groups, and .001 between Gal 12 mg bid and placebo groups, respectively.

For LOCF analysis, the ANOVA model with terms for treatment and center gave p-value .001, where centers with few patients were pooled together as in the OC analysis. The pairwise comparisons gave p-values .058 between Gal 4 mg bid and placebo groups, .001 between Gal 8 mg bid and placebo groups, and .001 between Gal 12 mg bid and placebo groups, respectively. The mean and mean change are presented in Table 4.6.1.2.

**Table 4.6.1.2 ADAS-cog/11: LOCF Case (Excluding Site)**

| | Placebo | | | Gal 4 mg bid | | | Gal 8 mg bid | | | Gal 12 mg bid | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Time Point | n | Mean ± SE | Mean Change ± SE | n | Mean ± SE | Mean Change ± SE | n | Mean ± SE | Mean Change ± SE | n | Mean ± SE | Mean Change ± SE |
| Month 5 | 255 | 30.9 ± 0.81 | 1.7 ± 0.43 | 126 | 28.3 ± 1.07 | 0.4 ± 0.52 | 253 | 27.5 ± 0.75 | -1.4 ± 0.35 | 253 | 27.3 ± 0.73 | -1.4 ± 0.39 |

## 4.6.2. Sponsor's Analyses on CIBIC-plus

The primary analysis was the observed case at month 5 of CIBIC-plus score. There were 237, 106, 212, and 212 patients at month 5 in placebo, Gal 4 mg bid, Gal 8 mg bid, and Gal 12 mg bid groups, respectively. There were 1 (0.4%), 0, 0, and 1 (0.5%) in markedly improved in placebo, Gal 4 mg bid, Gal 8 mg bid, and Gal 12 mg bid groups, respectively; 5 (2.1%), 2 (1.9%), 7 (3.3%), and 9 (4.2%) in moderately improved in placebo, groups, respectively; 19 (8.0%), 15 (14.2%), 38 (17.9%), and 41 (19.3%) in minimally improved in placebo, Gal 4 mg bid, Gal 8 mg bid, and Gal 12 mg bid groups, respectively; 87 (36.7%), 37 (34.9%), 98 (46.2%), and 85 (40.1%) in no change placebo, Gal 4 mg bid, Gal 8 mg bid, and Gal 12 mg bid groups, respectively; 85 (35.9%), 38 (35.8%), 51 (24.1%), and 59 (27.8%) in minimally worsened in placebo, Gal 4 mg bid, Gal 8 mg bid, and Gal 12 mg bid groups, respectively; 33 (13.9%), 14 (13.2%), 15 (7.1%), and 16 (7.5%) in moderately worsened in placebo, Gal 4 mg bid, Gal 8 mg bid, and Gal 12 mg bid groups, respectively; and 7 (3.0%), 0, 3 (1.4%), and 1 (0.5%) in markedly worsened in placebo, Gal 4 mg bid, Gal 8 mg bid, and Gal 12 mg bid groups, respectively.

The Van Elteren test controlling for center (pooled small centers together) gave p-value .001. The pairwise comparisons gave p-values .242 between Gal 4 mg bid and placebo, .001 between Gal 8 mg bid and placebo, and .001 between Gal 12 mg bid and placebo.

For LOCF analysis, there were 263, 128, 255, and 253 patients in placebo, Gal 4 mg bid, Gal 8 mg bid, and Gal 12 mg bid groups, respectively. The Van Elteren test controlling for center (pooled small centers together) gave p-value .001. The pairwise comparisons gave p-values .242 between Gal 4 mg bid and placebo, .001 between Gal 8 mg bid and placebo, and .001 between Gal 12 mg bid and placebo.

## 4.6.3. Sponsor's Analyses on Subgroups

The sponsor performed subgroup analyses based on sex, age, weight, baseline ADAS-cog/11, baseline MMSE, and so on. Table 4.6.3.1 and Table 4.6.3.2 present the analyses on sex, race, and age for ADAS-cog/11, and CIBIC-plus, respectively.

**Table 4.6.3.1 ADAS-cog/11 Subgroup Analyses at Month 5 (Excluding Site)**

| Subgroup | Placebo | | | Gal 4 mg bid | | | Gal 8 mg bid | | | Gal 12 mg bid | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Time Point | n | Mean | Mean Change | n | Mean | Mean Change | n | Mean | Mean Change | n | Mean | Mean Change |
| Female | 144 | 31.2 | 2.0 | 60 | 27.8 | 0.8 | 125 | 27.7 | -1.3 | 142 | 27.2 | -1.9 |
| Male | 81 | 28.7 | 1.5 | 41 | 26.6 | -0.8 | 83 | 25.7 | -1.8 | 69 | 25.7 | -1.7 |
| White | 208 | 30.2 | 1.8 | 97 | 27.6 | 0.2 | 194 | 27.0 | -1.5 | 195 | 26.6 | -1.7 |
| Non-white | 17 | 31.2 | 1.3 | 4 | 20.8 | -2.8 | 14 | 26.0 | -1.6 | 16 | 27.5 | -2.9 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Age<65 | 19 | 29.9 | 0.9 | 8 | 29.6 | 0.5 | 19 | 28.8 | -1.7 | 4 | 27.3 | -1.3 |
| Age 65-85 | 181 | 30.5 | 2.1 | 84 | 27.6 | 0.0 | 165 | 26.0 | -1.5 | 183 | 26.6 | -1.7 |
| Age>85 | 25 | 28.9 | -0.2 | 9 | 22.7 | 1.1 | 24 | 31.8 | -1.1 | 24 | 27.1 | -2.8 |

**Table 4.6.3.2 CIBIC-plus Subgroup Analyses at Month 5 (Excluding Site)**

| Subgroup | Placebo | | Gal 4 mg bid | | Gal 8 mg bid | | Gal 12 mg bid | |
|---|---|---|---|---|---|---|---|---|
| | n | Improved or no change | n | Improved or no change | n | Improved or no change | n | Improved or no change |
| Female | 151 | 73 (48.3%) | 65 | 32 (49.2%) | 129 | 91 (70.5%) | 143 | 90 (62.9%) |
| Male | 86 | 39 (45.3%) | 41 | 22 (53.7%) | 83 | 52 (62.7%) | 69 | 46 (66.7%) |
| White | 220 | 101 (45.9%) | 102 | 51 (50%) | 198 | 133 (67.2%) | 196 | 125 (63.8%) |
| Non-white | 17 | 11 (64.7%) | 4 | 3 (75%) | 14 | 10 (71.4%) | 16 | 11 (68.8%) |
| Age<65 years | 22 | 7 (31.8%) | 8 | 5 (62.5%) | 20 | 15 (75%) | 4 | 3 (75%) |
| Age 65-85 years | 188 | 87 (46.3%) | 89 | 44 (49.4%) | 168 | 112 (66.7%) | 184 | 119 (64.7%) |
| Age>85 years | 27 | 18 (66.7%) | 9 | 5 (55.6%) | 24 | 16 (66.7%) | 24 | 14 (58.3%) |

## 4.7. Reviewer's Analyses

### 4.7.1. Reviewer's Analyses on ADAS-cog

For OC analysis, this reviewer verified the sponsor's analysis, i.e., the ANOVA model with terms for treatment and center gives p-value .001. The pairwise comparisons give p-values .037 between Gal 4 mg bid and placebo groups, .001 between Gal 8 mg bid and placebo groups, and .001 between Gal 12 mg bid and placebo groups, respectively. Table 4.7.1.1 presents data from ' site.

**Table 4.7.1.1 ADAS-cog/11: Observed Case ( Site)**

| | Placebo | | | Gal 4 mg bid | | | Gal 8 mg bid | | | Gal 12 mg bid | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Time Point | n | Mean ± SD | Mean Change ± SD | n | Mean ± SD | Mean Change ± SD | n | Mean ± SD | Mean Change ± SD | n | Mean ± SD | Mean Change ± SD |
| Baseline | 10 | 23.0 ± 7.51 | | 6 | 27.0 ± 15.07 | | 11 | 17.7 ± 5.97 | | 11 | 20.3 ± 7.98 | |
| Month 5 | 5 | 20.2 ± 9.65 | -4.2 ± 5.02 | 2 | 13.0 ± 0 | -7.5 ± 4.95 | 3 | 13.7 ± 6.66 | -7.7 ± 4.73 | 3 | 18.0 ± 6.08 | -3.7 ± 5.03 |

Table 4.7.1.2 presents ADAS-cog/11 at month 5 after including site.

**Table 4.7.1.2 ADAS-cog/11: Observed Case (Including Site)**

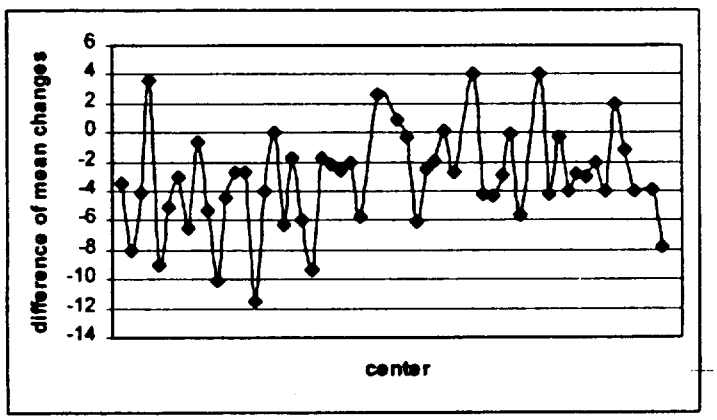
| | Placebo | | | Gal 4 mg bid | | | Gal 8 mg bid | | | Gal 12 mg bid | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Time | n | Mean | Mean | n | Mean | Mean | n | Mean | Mean | n | Mean | Mean |

| Point | | ± SD | Change ± SD | | ± SD | Change ± SD | | ± SD | Change ± SD | | ± SD | Change ± SD |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline | 279 | 29.2 ± 10.28 | | 137 | 27.7 ± 10.92 | | 276 | 28.9 ± 10.80 | | 272 | 28.6 ± 10.82 | |
| Month 5 | 230 | 30.1 ± 12.75 | 1.7 ± 6.49 | 103 | 27.0 ± 11.30 | -0.04 ± 5.92 | 211 | 26.7 ± 12.26 | -1.6 ± 5.79 | 214 | 26.6 ± 11.39 | -1.9 ± 6.35 |

After including site, the ANOVA model with terms for treatment and center gives p-value .0001, where centers with few patients are pooled together. The pairwise comparisons give p-values .0308 between placebo and Gal 4 mg bid, .0001 between placebo and Gal 8 mg bid, and .0001 between placebo and Gal 12 mg bid.

Figure 4.7.1 presents the difference of mean changes between Gal (combining Gal 4 mg bid, 8 mg bid, and 16 mg bid) and placebo. A negative value indicates that Gal is numerically superior to placebo.

**Figure 4.7.1 ADAS-cog: Difference of Mean Changes by Center**




Among 53 centers, 45 of 53 show that Gal is numerically superior to placebo. The difference of mean changes of Centers 11, 15, and 21 are larger. In Center 11, there are 3, 2, 1, and 4 patients in placebo, Gal 4 mg bid, 8 mg bid, and 12 mg bid groups, respectively. The mean changes are 3.67, -4, -6, and -7.75, respectively. In Center 15, there are 1, and 2 patients in placebo, and Gal 12 mg bid groups, respectively. The mean changes are 7.0, and –4.5, respectively. In Center 21, there are 2, 1, 2, and 2 patients in placebo, Gal 4 mg bid, 8 mg bid, and 12 mg bid groups, respectively. The mean changes are 6.5, 1.0, -12, and 6.5, respectively.

For LOCF analysis, this reviewer verified the sponsor's analysis, i.e., the ANOVA model with terms for treatment and center gives p-value .001. The pairwise comparisons give p-values .058 between Gal 4 mg bid and placebo groups, .001 between Gal 8 mg bid and placebo groups, and .001 between

Gal 12 mg bid and placebo groups, respectively. After including site, the ANOVA model with terms for treatment and center gives p-value .0001, where centers with few patients are pooled together. The pairwise comparisons give p-values .0712 between placebo and Gal 4 mg bid, .0001 between placebo and Gal 8 mg bid, and .0001 between placebo and Gal 12 mg bid.

**Table 4.7.1.3 ADAS-cog/11: LOCF Case (Including Site)**

| | Placebo | | | Gal 4 mg bid | | | Gal 8 mg bid | | | Gal 12 mg bid | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Time Point | n | Mean ± SD | Mean Change ± SD | n | Mean ± SD | Mean Change ± SD | n | Mean ± SD | Mean Change ± SD | n | Mean ± SD | Mean Change ± SD |
| Month 5 | 265 | 30.6 ± 12.89 | 1.5 ± 6.28 | 132 | 28.1 ± 12.38 | 0.4 ± 5.94 | 262 | 27.0 ± 12.05 | -1.5 ± 5.47 | 264 | 26.9 ± 11.61 | -1.5 ± 6.11 |

Table 4.7.1.4 presents the dropouts for placebo and Gal (combining Gal 4, 8 and 12 mg bid together) at Month 3 and Month 5. There is no bias shown in the dropouts.

**Table 4.7.1.4 ADAS-cog/11: Dropouts (Including Site)**

| Dropout at | Dropout number | Baseline Mean ± SD | Week 4 Mean ± SD | Month 3 Mean ± SD |
|---|---|---|---|---|
| Month 3 | Gal 65 | 28.4 ± 12.2 | 28.1 ± 12.1 | |
| | Pla 19 | 30.4 ± 10.6 | 30.1 ± 12.7 | |
| Month 5 | Gal 65 | 29.7 ± 11.5 | 29.0 ± 13.1 | 29.3 ± 13.5 |
| | Pla 16 | 36.3 ± 10.1 | 35.3 ± 11.8 | 37.6 ± 13.3 |

## 4.7.2. Reviewer's Analyses on CIBIC-plus

In the sponsor's OC analysis (excluding site), there were 237, 106, 212, and 212 patients at month 5 in placebo, Gal 4 mg bid, Gal 8 mg bid, and Gal 12 mg bid groups, respectively. This reviewer only has 235, 105, 212, and 212 patients in the corresponding groups, respectively. This reviewer thought that the sponsor included the patients A73359 (in placebo group), A74103 (in placebo group), and A73511 (in Gal 4 mg bid group) in their analysis, who were not marked as ITT in the data set. Using 235, 105, 212, and 212 patients, the mean ± SD at month 5 for CIBIC-plus are presented in Table 4.7.2.1.

**Table 4.7.2.1 CIBIC-plus: Observed Case (Excluding Site)**

| | Placebo | | Gal 4 mg bid | | Gal 8 mg bid | | Gal 12 mg bid | |
|---|---|---|---|---|---|---|---|---|
| Time Point | n | Mean ± SD | n | Mean ± SD | n | Mean ± SD | n | Mean ± SD |
| Month 5 | 235 | 4.59 ± 1.02 | 105 | 4.44 ± 0.96 | 212 | 4.18 ± 0.97 | 212 | 4.15 ± 1.01 |

The Van Elteren test controlling for center gives p-value .001. The pairwise comparisons give p-values .231 between Gal 4 mg bid and placebo, .001 between Gal 8 mg bid and placebo, and .001 between Gal 12 mg bid and placebo.

**Table 4.7.2.2 CIBIC-plus: Observed Case ( Site)**

| | Placebo | | Gal 4 mg bid | | Gal 8 mg bid | | Gal 12 mg bid | |
|---|---|---|---|---|---|---|---|---|
| Time Point | n | Mean ± SD | n | Mean ± SD | n | Mean ± SD | n | Mean ± SD |
| Month 5 | 5 | 3.80 ± 0.45 | 3 | 4.0 ± 0 | 3 | 4.0 ± 0 | 3 | 3.67 ± 0.58 |

Table 4.7.2.3 presents CIBIC-plus at month 5 after including site.

**Table 4.7.2.3 CIBIC-plus: Observed Case (Including Site)**

| | Placebo | | Gal 4 mg bid | | Gal 8 mg bid | | Gal 12 mg bid | |
|---|---|---|---|---|---|---|---|---|
| Time Point | n | Mean ± SD | n | Mean ± SD | n | Mean ± SD | n | Mean ± SD |
| Month 5 | 240 | 4.57 ± 1.02 | 108 | 4.43 ± 0.95 | 215 | 4.18 ± 0.96 | 215 | 4.14 ± 1.00 |

After including site, the Van Elteren test controlling for center gives p-value .001. The pairwise comparisons give p-values .265 between Gal 4 mg bid and placebo, .001 between Gal 8 mg bid and placebo, and .001 between Gal 12 mg bid and placebo.

In the sponsor's LOCF analysis (excluding . site), there were 263, 128, 255, and 253 patients at month 5 in placebo, Gal 4 mg bid, Gal 8 mg bid, and Gal 12 mg bid groups, respectively. This reviewer only has 260, 127, 255, and 253 patients in the corresponding groups, respectively. This reviewer thought that the sponsor included the patients A73178 (in placebo group), A73359 (in placebo group), A74103 (in placebo group), and A73511 (in Gal 4 mg bid group) in their analysis, who were not marked as ITT in the data set. Using 260, 127, 255, and 253 patients, the mean ± SD at month 5 for CIBIC-plus are presented in Table 4.7.2.4.

**Table 4.7.2.4 CIBIC-plus: LOCF Case (Excluding . Site)**

| | Placebo | | Gal 4 mg bid | | Gal 8 mg bid | | Gal 12 mg bid | |
|---|---|---|---|---|---|---|---|---|
| Time Point | n | Mean ± SD | n | Mean ± SD | n | Mean ± SD | n | Mean ± SD |
| Month 5 | 260 | 4.55 ± 1.01 | 127 | 4.42 ± 0.99 | 255 | 4.21 ± 0.95 | 253 | 4.17 ± 0.99 |

The Van Elteren test controlling for center gives p-value .001. The pairwise comparisons give p-values .260 between Gal 4 mg bid and placebo, .001 between Gal 8 mg bid and placebo, and .001 between Gal 12 mg bid and placebo.

For LOCF analysis, after including site, the Van Elteren test controlling for center gives p-value .001. The pairwise comparisons give p-values .221 between Gal 4 mg bid and placebo, .001 between Gal 8 mg bid and placebo, and .001 between Gal 12 mg bid and placebo.

**Table 4.7.2.5 CIBIC-plus: LOCF Case (Including Site)**

| | Placebo | | Gal 4 mg bid | | Gal 8 mg bid | | Gal 12 mg bid | |
|---|---|---|---|---|---|---|---|---|
| Time Point | n | Mean ± SD | n | Mean ± SD | n | Mean ± SD | n | Mean ± SD |
| Month 5 | 270 | 4.53 ± 1.00 | 133 | 4.39 ± 0.98 | 264 | 4.20 ± 0.94 | 264 | 4.16 ± 0.97 |

### 4.7.3. Reviewer's Analyses on Subgroups

This reviewer verified the sponsor's analysis. This reviewer thought that the sponsor included the patients A73359, A74103, A73511 in CIBIC-plus analysis who were not marked as ITT in the data set. See details in Section 4.6.3.

## 4. Conclusion

Based on the analysis, both GAL-INT-1 and GAL-USA-1 provide nominally statistically significant evidence that 12 mg bid or 16 mg bid galantamine-treated patients had a greater mean change of ADAS-cog/11 total score from baseline to Month 6 than that placebo-treated patients had, and had a smaller mean CIBIC-plus score at Month 6 than that placebo-treated patients had.

Based on the analysis, GAL-USA-10 provides nominally statistically significant evidence that 8 mg bid or 12 mg bid galantamine-treated patients had a greater mean change of ADAS-cog/11 total score from baseline to Month 5 than that placebo-treated patients had, and had a smaller mean CIBIC-plus score at Month 5 than that placebo-treated patients had. GAL-USA-10 also provides nominally statistically significant evidence that 4 mg bid galantamine-treated patients had a greater mean change of ADAS-cog/11 total score from baseline to Month 5 than that placebo-treated patients had. Although 4 mg bid galantamine-treated patients had a smaller mean CIBIC-plus score at Month 5, it is not nominally statistically significant.

For GAL-USA-1, conclusions on the significance are the same between including and excluding the data from site. For GAL-USA-10, conclusions on the significance are the same between including and excluding the data from site.

/S/

Kun He
Statistical Reviewer

Concur:

/S/

Kun Jin, Ph.D.
Team Leader

/S/

George Chi, Ph.D.
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Arch. NDA 21-169 (Galantamine)

HFD-120
HFD-120/Dr. Katz
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HFD-710/Dr. Chi
HFD-710/Dr. Jin
HFD-710/Dr. He

# Statistical Review and Evaluation of Carcinogenicity



| | |
|---|---|
| NDA #: | 21-169 |
| Sponsor: | Janssen Research Foundation |
| Drug: | REMINYL (galantamine) Tablets |
| Statistical Reviewer: | Kallappa M. Koti |
| Pharmacologist: | Barry Rosloff, Ph.D. |

**Table of Contents**



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This reviewer is very grateful to Mrs. Roswitha Kelly without whose help this review was not possible.

## 1. Introduction

In this NDA submission two animal carcinogenicity studies, one in mice and one in rats, were included. The objective of these studies was to evaluate the carcinogenic potential of R113675 (galantamine) in rats and mice when administered orally at some selected dose levels. The length of these studies was two years for both rats and mice.

This reviewer independently performed analysis on the survival and tumor data. The background for these analyses is found in Lin and Ali (1995). The purpose of the survival analysis were: (1) to examine the significance of the differences in survival among the treatment groups (i.e., homogeneity test), and (2) to determine the significance of positive or negative dose-mortality trend (i.e., dose-mortality trend test). The Cox test statistic and the generalized Kruskal-Wallis test statistic were used.

In the tumor data analysis, the tumors were classified as either fatal (lethal) or incidental. In the analysis for a selected tumor, the significance of dose-tumor positive linear trend was the primary interest. Using the Peto's (see Lin and Ali, 1995) method, the death-rate method for fatal tumors and prevalence method for incidental tumors were applied. The p-values of these tests were evaluated by an exact permutation method. For tumors that caused deaths for some, but not all animals, a combined test was performed. The combined test used the Z-statistic which is assumed to follow the standard normal distribution. This test was referred to as the asymptotic test in the following context. To adjust p-values for the effect of multiple testing, a rule proposed by the Division of Biometrics, CDER/FDA was used in the review. This rule says that in order to keep the false-positive rate at the nominal level of approximately 0.1, tumor types with a spontaneous tumor rate of $\leq 1\%$ (rare tumor) should be tested at 0.025 significance level, otherwise (common tumor) a 0.005 significance level should be used.
When a tumor occurred only as fatal or only as incidental in the animals this reviewer used an exact permutation trend test or exact permutation pair-wise comparison. When a tumor occurred in both the fatal and incidental context, an approximation to the exact test is used.

In this review, the reviewer's analyses is performed using a software called- "carcin" written by Dr. Ted Guo of CDER/FDA.

## 1. STUDY 4199: The Mouse Study

### 2.1 Design and sponsor's results

480 SPF Albino Swiss CD1 mice were randomly assigned to groups given R113675 (galantimine) daily by the oral gavage route as shown in Table 2.1 below. Galantamine was administered to male mice for approximately 105 weeks and to female mice for approximately 104 weeks at dosages of 2.5, 5 or 5/7.5/10 mg/kg. Ten mg/kg was given to 10 male and 10 female mice of the high dosage group on day 0 (March 20, 1997), which

resulted in mortality in 3 female mice. All males and the remaining females of this dosage group were then dosed at 5 mg/kg from March 20, 1997 till April 1, 1997 and at 7.5 mg/kg from April 2, 1997 till April 15, 1997. The dosage in this group was then increased up to 10 mg/kg from April 16, 1997 onwards till the end of the study. The high dosage group will be referred to as the 10 mg/kg dosage group. Surviving males and females were sacrificed in week 105 and week 104, respectively. Animal 842 which was discarded in error, was not included in the database for statistical analysis.

Table 2.1: Number of animals by sex and dose

| | Dose level (mg/kg/day) | | | | |
|---|---|---|---|---|---|
| Sex | 0 (Control) | 2.5 | 5 | 10 | Total |
| Males | 60 | 60 | 60 | 60 | 240 |
| Females | 60 | 60 | 60 | 60* | 240 |

* One female was discarded by accident.

Sponsor's survival analyses

In males, 128 animals died before the terminal sacrifice, 30 in the first year of the study. In females, 154 animals died before the terminal sacrifice, 26 in the first year of study. In both sexes, the number of animals dying before terminal sacrifice was lower in each of the treated groups than in the control group. The lower mortality was, however, not significant at $p < 0.05$ in any of the pair-wise comparisons with the control group or in the trend analysis. The trend was, however, significant at $p < 0.1$ for females in both Peto and Kruskal-Wallis analyses. The differences in mortality, which can be seen in the Kaplan-Meier plots, are taken into account in the tumor analyses that follow. Cross classifications of number of dead male and female mice are given in Table 2.2 and Table 2.3, respectively.

Table 2.2: Statistical analysis of survival of male mouse
(Number of animals dead)

| | Dose level (mg/kg/day) | | | | |
|---|---|---|---|---|---|
| Grouped week of death | 0 | 2.5 | 5 | 10 | Total |
| Died in weeks 1 to 52 | 7 | 6 | 8 | 9 | 30 |
| Died in weeks 53 to 73 | 6 | 5 | 8 | 9 | 28 |
| Died in weeks 74 to 86 | 7 | 7 | 4 | 5 | 23 |
| Died in weeks 87 to 94 | 10 | 4 | 1 | 3 | 18 |
| Died in weeks 95 to 104 | 8 | 5 | 9 | 7 | 29 |
| Sacrifice in week 105 | 22 | 33 | 30 | 27 | 112 |
| Total | 60 | 60 | 60 | 60 | 240 |

Table 2.3: Statistical analysis of survival of female mouse
(Number of animals dead)

| Grouped week of death | Dose level (mg/kg/day) 0 | 2.5 | 5 | 10 | Total |
|---|---|---|---|---|---|
| Died in weeks 1 to 52 | 9 | 3 | 8 | 6 | 26 |
| Died in weeks 53 to 73 | 8 | 11 | 10 | 6 | 35 |
| Died in weeks 74 to 86 | 10 | 10 | 7 | 7 | 34 |
| Died in weeks 87 to 94 | 10 | 5 | 4 | 5 | 24 |
| Died in weeks 95 to 103 | 8 | 11 | 4 | 12 | 35 |
| Sacrifice in week 104 | 15 | 20 | 27 | 23 | 85 |
| Total | 60 | 60 | 60 | 59 | 239 |

There were no relevant adverse changes in mortality rate in males of the 2.5, 5 and 10 mg/kg dosage groups and in females of the 2.5 mg/kg dosage group compared with that of the control group. A tendency in reduced mortality was seen in females dosed at 5 and 10 mg/kg.
A decreased incidence of bad condition was observed in male mice dosed at 2.5 mg/kg. There were no adverse clinical effects in female mice dosed at 2.5 mg/kg. Body weight and weight gain were marginally decreased in male and female mice of this dosage group. Organ weights were not adversely affected in male mice whereas a slight decrease in absolute weight of the pancreas was seen in female mice of this dosage group. Food consumption, hematology, serum analysis and gross pathology were not adversely affected in male nor female mice dosed at 2.5 mg/kg.
In male mice dosed at 5 mg/kg, the incidence of bad condition was decreased. In female mice dosed at 5 mg/kg the incidence in cachexia was decreased. Body weight of male mice dosed at 5 mg/kg was decreased with about 10%, weight gain was decreased with more than 20%. Only a slight decrease in body weight and weight gain was seen in the females of this dosage group.
In the 10 mg/kg dosage group, sedation was observed in all male and female mice from week 4 onwards (after the increase of the dose up to 10 mg/kg) through out the dosing period. The administration of 2.5, 5 and 10 mg/kg of galantamine did not result in an increased incidence of tumor-bearing mice or in an increase in any tumor-type.

Histopathological examination was carried out as follows.
Control and all dosed animals: Adrenal glands, epididymides, gall bladder, kidneys, liver, lungs, lymph node (mesenteric), mammary gland, overies, pancreas, pituitary gland, salivary gland (submandibular), spleen, testes, thymus, uterus, bagina and any organ or tissue with a neoplasm suspected at most mortem examination.
Controls and high dosed animals: Bone (sternum), bone (stifle joint), bone marrow, brain, coagulating glands, esophagus, heart, parathyroid glands, prostate, seminal vesicles, stomach (fore), stomach (glandular), thyroid glands, trachea and urinary bladder.

Tumor incidence
The most commonly occurring tumors seen were primary lung tumors (in 99 animals, 16 fatal), liver hepatocellular tumors (65 cases, 9 fatal), mesenchymal tumors of oviduct-

uterus and uterine cervix-vagina (28 cases, 2 fatal), histiocytic sarcoma (22 cases, 17 fatal), and malignant lymphoma (18 cases, 7 fatal). Some other tumors of moderate incidence (at least three cases)- adrenal phaeochromocytoms, liver haemangiomas, ovarian adenomas, ovarian granulosa-theca cell tumors and thyroid follicular adenomas- were always classified as incidental to death, but fatal tumors were reported among lymphoid leukaemias, myeloid leukaemias, pituitary adenomas, spleen vascular tumors, soft tissue sarcomas, testis benign Leydig-cell tumors and uterine epithelial tumors.

Sponsor's summary of conclusions

In a carcinogenicity study of 480 SPF Albino Swiss CD1 mice given R113675 (galanamine) by gavage at doses of 0, 2.5, 5 and 10 mg/kg/day, there was no evidence at all of an adverse effect of treatment on tumor incidence.

Treatment was associated with a decreased overall incidence of benign and malignant tumors in both sexes. The reduction was evident to a similar extent at all three dose levels tested. The main tumor types contributing to this decrease were liver hepatocellular tumors, lung carcinomas, spleen vascular neoplasia and malignant lymphoma.

Although no adverse effect of treatment on tumor incidence was seen in males or females, the study was adequate in terms of survival to detect a possible effect in either sex.

## The Reviewer's Analyses

2.2 Survival Data Analysis

This reviewer confirmed sponsor's results on mortality. Analyses of mortality for males and females are presented in Table 2.4 and Table 2.5, respectively.

Table 2.4: **Analysis of Mortality**
Species: Mouse
Sex: Male

| DOSE | Numbers and cum. % | WEEK | | | | |
|---|---|---|---|---|---|---|
| | | 0 - 52 | 53 - 78 | 79 - 91 | 92 - 104 | 105 - 106 |
| CTRL | Number of Dead | 7 | 8 | 10 | 13 | 22 |
| | Number at Risk | 60 | 53 | 45 | 35 | 60 |
| | Cumulative % Died | 11.7 | 25.0 | 41.7 | 63.3 | 36.7 |
| LOW | Number of Dead | 6 | 6 | 8 | 7 | 33 |
| | Number at Risk | 60 | 54 | 48 | 40 | 60 |
| | Cumulative % Died | 10.0 | 20.0 | 33.3 | 45.0 | 55.0 |
| MED | Number of Dead | 8 | 8 | 5 | 9 | 30 |
| | Number at Risk | 60 | 52 | 44 | 39 | 60 |
| | Cumulative % Died | 13.3 | 26.7 | 35.0 | 50.0 | 50.0 |
| HIGH | Number of Dead | 9 | 10 | 6 | 8 | 27 |
| | Number at Risk | 60 | 51 | 41 | 35 | 60 |
| | Cumulative % Died | 15.0 | 31.7 | 41.7 | 55.0 | 45.0 |

Table 2.5: **Analysis of Mortality**
Species: Mouse
Sex: Female

| DOSE | Numbers and cum. % | WEEK | | | | |
|---|---|---|---|---|---|---|
| | | 0 - 52 | 53 - 73 | 73- 86 | 87 - 103 | 104 - 104 |
| CTRL | Number of Dead | 9 | 8 | 10 | 18 | 15 |
| | Number at Risk | 60 | 51 | 43 | 33 | 60 |
| | Cumulative % Died | 15.0 | 28.3 | 45.0 | 75.0 | 25.0 |
| LOW | Number of Dead | 3 | 11 | 10 | 16 | 20 |
| | Number at Risk | 60 | 57 | 46 | 36 | 60 |
| | Cumulative % Died | 5.0 | 23.3 | 40.0 | 66.7 | 33.3 |
| MED | Number of Dead | 8 | 10 | 7 | 8 | 27 |
| | Number at Risk | 60 | 52 | 42 | 35 | 60 |
| | Cumulative % Died | 13.3 | 30.0 | 41.7 | 55.0 | 45.0 |
| HIGH | Number of Dead | 6 | 6 | 7 | 17 | 23 |
| | Number at Risk | 59 | 53 | 47 | 40 | 59 |
| | Cumulative % Died | 10.2 | 20.3 | 32.2 | 61.0 | 39.0 |

Results of Cox and Kruskal-Wallis methods on dose-mortality trends for males and females are as follows.

Table 2.6: **Dose-Mortality Trend Tests**

| Method | Time-Adjusted Trend Test | Male | | Female | |
|---|---|---|---|---|---|
| | | Statistic | p-value | statistic | p-value |
| Cox | Dose-Mortality Trend | 0.00 | 0.9583 | 2.10 | 0.1477 |
| | Depart from Trend | 3.58 | 0.1671 | 2.92 | 0.2318 |
| | Homogeneity | 3.58 | 0.3103 | 5.02 | 0.1704 |
| Kruskal-Wallis | Dose-Mortality Trend | 0.10 | 0.7572 | 1.97 | 0.1608 |
| | Depart from Trend | 2.79 | 0.2477 | 1.95 | 0.3780 |
| | Homogeneity | 2.89 | 0.4094 | 3.91 | 0.2711 |

## 2.3 Tumor Data Analysis

This reviewer confirmed sponsor's results on tumor incidence. There were no statistically significant positive linear trends detected in both female and male mice. Details are shown in Table A.1 and Table A.2.

## 3. STUDY 4101: The Rats Study

### 3.1 Design and sponsor's results

480 SPF Wistar rats were randomly assigned to groups given R113675 (galantamine) daily by oral gavage route as shown in Table 3.1 below. Galantamine was administered orally by gavage to rats for 24 months at dosages of 2.5, 10 and 40/20/30 mg/kg. In the high dosage group, rats were dosed at 40 mg/kg for 1 day, which resulted in mortality in 3 out of 60 males and in 12 out of 60 female rats. After a recovery of 3 days in this dosage group, the male and female rats were dosed at 20 mg/kg. The dosage was increased up to 30 mg/kg from week 4 onwards in the male rats and from week 10 onwards in the female rats, for the remaining part of the study.

Table 3.1: Number of animals by sex and dose

| | Dose level (mg/kg/day) | | | | |
|---|---|---|---|---|---|
| Sex | 0 (Control) | 2.5 | 10 | 30 | Total |
| Males | 60 | 60 | 60 | 60 | 240 |
| Females | 60 | 60 | 60 | 60 | 240 |

Sponsor's survival analyses

In males, 96 animals died before the terminal sacrifice, 33 in the first year of the study. In females, 99 animals died before the terminal sacrifice, 13 in the first year of the study. In both sexes, the pattern of survival in relation to treatment was similar. Thus, compared to the control, survival was slightly but non-significantly better at 2.5 mg/kg/day, significantly better at 10 mg/kg/day ($p<0.05$ in both sexes for Peto fatal analysis, $p<0.001$ in males and $p<0.01$ in female for Kruskal-Wallis analysis), but was not significantly affected at 30 mg/kg/day. The differences in mortality, which can also be seen in the Kaplan-Meier plots, are taken into account in the tumor analyses that follow. Cross classifications of number of dead male and female animals are given in Table 3.2 and Table 3.3, respectively.

Table 3.2: Statistical analysis of survival of male rats
(Number of animals dead)

| | Dose level (mg/kg/day) | | | | |
|---|---|---|---|---|---|
| Grouped week of death | 0 | 2.5 | 10 | 30 | Total |
| Died in weeks 1 to 52 | 9 | 8 | 4 | 12 | 33 |
| Died in weeks 53 to 74 | 3 | 4 | 4 | 9 | 20 |
| Died in weeks 75 to 87 | 4 | 7 | 1 | 5 | 17 |
| Died in weeks 88 to 95 | 4 | 1 | 2 | 2 | 9 |
| Died in weeks 96 to 104 | 7 | 2 | 4 | 4 | 17 |
| Sacrifice in week 105-106 | 33 | 38 | 45 | 28 | 144 |
| Total | 60 | 60 | 60 | 60 | 240 |

Table 3.3: Statistical analysis of survival of female rats
(Number of animals dead)

| Grouped week of death | Dose level (mg/kg/day) 0 | 2.5 | 10 | 30 | Total |
|---|---|---|---|---|---|
| Died in weeks 1 to 52 | 4 | 4 | 1 | 4 | 13 |
| Died in weeks 53 to 74 | 6 | 3 | 3 | 4 | 16 |
| Died in weeks 75 to 87 | 2 | 6 | 3 | 3 | 14 |
| Died in weeks 88 to 95 | 10 | 5 | 4 | 9 | 28 |
| Died in weeks 96 to 104 | 7 | 8 | 6 | 7 | 28 |
| Sacrifice in week 105-106 | 31 | 34 | 43 | 33 | 141 |
| Total | 60 | 60 | 60 | 60 | 240 |

In female rats, a negative trend was noted in the incidences of animals bearing incidental and of animals bearing fatal and/or incidental tumors.

Tumor incidence

The most commonly occurring tumors seen were pituitary adenomas (in 156 animals, 44 fatal), mammary tumors (38 cases, 7 fatal), thyroid follicular tumors (28 cases, none fatal), uterine adenocarcinomas (25 cases, 10 fatal), uterine stromal polyps (24 cases, none fatal), and thyroid C-cells tumors (22 cases, none fatal). Many other tumors of moderate incidence (at least 3 cases)- adrenal cirtex adenomas, liver hepatocellular tumors, lymph node hemangiomas, lymphosarcomas, ovarian granulosa theca-cell tumors, pancreas endocrine tumors, and testis Leydig cell tumors and thymomas- were always classified as incidental to death, but fatal tumors were reported among adrenal medullary phaecochromocytomas, lymphoid leukaemias, uterine carcinomas, uterine sarcomas/fibrosarcomas, external ear squamous carcinomas, cervix carcinomas, cervix sarcomas, squamous skin tumors and soft tissue fiber tumors.

Tumor-increasing effects of treatment

For only two tumors, uterine adenocarcinomas and cervix sarcomas, was there any evidence whatsoever of a positive effect of treatment, as judged by a one-tailed trend with $p<0.05$.

Tumor-reducing effects of treatment

There was evidence that treatment was associated with a reduced incidence of mammary tumors, pituitary and overall tumor incidence, as judged by a two-tailed trend with $p<.05$.

Overall tumor incidence

Malignant tumors were seen in 26 males and 62 females. In males, incidence was very similar in each group, but in females, incidence was rather higher at 10 mg/kg/day and at 30 mg/kg/gay than in the controls, reflecting to some extent the findings already noted for uterine adenocarcinomas and for cervix sarcomas. However, neither the trend nor nay pairwise differences from the control were significant for overall malignant tumor incidence.

Sponsor's summary of conclusions

In a carcinogenecity study of 480 SPF Wistar rats given R113675 (galantamine) in diet at doses of 0, 2.5, 10 and 30 mg/kg/day, no clear evidence of an adverse effect of treatment on tumor incidence was seen. Treatment was clearly associated with a decreased incidence of mammary tumors in females at 30 mg/kg/day and of pituitary adenomas in both sexes at 10 mg/kg/day and at
30 mg/kg/day. Although no clear adverse effect of treatment on tumor incidence was seen in males or females, the study was adequate in terms of survival to detect a possible effect in either sex.

**The Reviewer's analyses**

3.2 Survival Data Analysis

This reviewer confirmed sponsor's results on mortality. Analyses of mortality for males and females are presented in Table 2.4 and Table 3.5, respectively.

Table 3.4: **Analysis of Mortality**
Species: Rat
Sex: Male

| DOSE | Numbers and cum. % | WEEK | | | | |
|---|---|---|---|---|---|---|
| | | 0 - 52 | 53 - 78 | 79 - 91 | 92 - 104 | 105 - 106 |
| CTRL | Number of Dead | 9 | 4 | 5 | 8 | 34 |
| | Number at Risk | 60 | 51 | 47 | 42 | 60 |
| | Cumulative % Died | 15.0 | 21.7 | 30.0 | 43.3 | 56.7 |
| LOW | Number of Dead | 8 | 7 | 5 | 2 | 38 |
| | Number at Risk | 60 | 56 | 45 | 40 | 60 |
| | Cumulative % Died | 13.3 | 25.0 | 33.3 | 36.7 | 63.3 |
| MED | Number of Dead | 4 | 4 | 3 | 4 | 45 |
| | Number at Risk | 60 | 56 | 52 | 49 | 60 |
| | Cumulative % Died | 6.7 | 13.3 | 18.3 | 25.0 | 75.0 |
| HIGH | Number of Dead | 12 | 10 | 4 | 6 | 28 |
| | Number at Risk | 60 | 48 | 38 | 34 | 60 |
| | Cumulative % Died | 20.0 | 36.7 | 43.3 | 53.3 | 46.7 |

Table 3.5: **Analysis of Mortality**
Species: Rat
Sex: Female

| DOSE | Numbers and cum. % | WEEK | | | | |
|---|---|---|---|---|---|---|
| | | 0 - 52 | 53 - 78 | 79 - 91 | 92 - 104 | 105 - 106 |
| CTRL | Number of Dead | 4 | 6 | 10 | 9 | 31 |
| | Number at Risk | 60 | 56 | 50 | 40 | 60 |
| | Cumulative % Died | 6.7 | 16.7 | 33.3 | 48.3 | 51.7 |

| | | | | | | |
|---|---|---|---|---|---|---|
| LOW | Number of Dead | 4 | 4 | 8 | 10 | 34 |
| | Number at Risk | 60 | 56 | 52 | 44 | 60 |
| | Cumulative % Died | 6.7 | 13.3 | 26.7 | 43.3 | 56.7 |
| MED | Number of Dead | 1 | 5 | 3 | 7 | 44 |
| | Number at Risk | 60 | 59 | 54 | 51 | 60 |
| | Cumulative % Died | 1.7 | 10.0 | 15.0 | 26.7 | 73.3 |
| HIGH | Number of Dead | 4 | 4 | 11 | 7 | 34 |
| | Number at Risk | 60 | 56 | 52 | 41 | 60 |
| | Cumulative % Died | 6.7 | 13.3 | 31.7 | 43.3 | 56.7 |

Results of Cox and Kruskal-Wallis methods on dose-mortality trends for males and females are as follows.

Table 3.6: **Dose-Mortality Trend Tests**

| Method | Time-Adjusted Trend Test | Male | | Female | |
|---|---|---|---|---|---|
| | | Statistic | p-value | statistic | p-value |
| Cox | Dose-Mortality Trend | 3.52 | 0.0606 | 0.06 | 0.8038 |
| | Depart from Trend | 7.61 | 0.0222 | 6.38 | 0.0412 |
| | Homogeneity | 11.14 | 0.0110 | 6.44 | 0.0920 |
| Kruskal-Wallis | Dose-Mortality Trend | 3.45 | 0.0631 | 0.04 | 0.8329 |
| | Depart from Trend | 7.69 | 0.0214 | 6.36 | 0.0416 |
| | Homogeneity | 11.15 | 0.0110 | 6.40 | 0.0936 |

## 3.3 Tumor Data Analysis

The p-values of the tested tumor types for male and female rats are given in Tables A.3 and Table A.4 of Section 6, respectively. In female rats of control group 0/60 rats had cervix sarcoma tumor and 4/60 had uterus adenocarcinoma. The tumor trend test for cervix sarcoma tumor (which is observed to be rare) is statistically significant ( asymptotic p-value=0.0021). The exact permuation test (for cervix sarcoma) for comparing the "high" dose of galantamine and control is statistically significant (p-value = 0.0468). However, as the number of tumors is small this p-value may not be stable. The tumor trend test for uterus adenocarcinoma (which is observed to be common) is not statistically significant (asymptotic p-value = 0.0155). The tumor trend test for cervix carcinoma adenosquam (which is only fatal) is not statistically significant (exact p-value = 0.0604). The tumor trend test for uterus adenocarcinoma (which is observed to be common) is not statistically significant (asymptotic p-value = 0.0155). Dose-tumor trend test for "high" dose of galantamine versus control in case of uterus adenocarcinoma is not statistically significant (asymptotic p-value = 0.0483).

## 4. Evaluation of validity of design

To evaluate the validity of experimental design of carcinogenicity studies, the CDER statisticians usually consider two issues: (1) Were enough animals exposed, for a sustained amount of time, to the risk of late developing tumor? (2) Were dose levels high enough to pose a reasonable tumor challenge to the animals? The following rules of thumb regarding these issues are suggested.

For sexes where no adverse tumorigenic effect of treatment is evident, it is necessary to determine whether the study was in fact adequate in terms of survival to detect such an effect. According to Haseman (1984) a 50% survival of initial animals in the high dose group between weeks 80-89 is considered as a sufficient number and adequate exposure.
As far as the adequacy of dose level is considered, it is generally accepted that the high dose should be close to the MTD (maximum tolerated dose). Chu et al. (1981) proposed the following criteria: (1) A dose is considered adequate if there is a detectable loss in weight gain of up to 10% in a dosed group relative to the controls. (2) The administered dose is also considered an MTD if dosed animals exhibit clinical signs or severe histopathologic toxic effects attributed to the chemical.

In Study 4199, no tumorigenic effect of treatment was seen in either sex, so criteria for adequacy are considered in both sexes. There were 60 high dose males with a median survival of 98 weeks and 59 high dose females with a median survival of 99 weeks, so survival is considered adequate.
In Study 4101, no tumorigenic effect of treatment was seen in males and no clear tumorigenic effect was seen in females, so criteria for adequacy are considered in both sexes. Over half (33) of the 60 high dose females survived to the terminal sacrifice starting at week 105, and almost half (28) of the high dose males did (median survival 100 weeks), so survival is considered adequate.

## 5. Conclusions

5.1 Study 4199- Mice

- For both female and male mice, the differences in survival among the four groups were not statistically significant, and there were no statistically significant dose-mortality trends.
- Tumor data analysis does not show any statistically significant positive linear trend in both female and male mice.
- According to the Haseman's (1984) criterion, the study design is adequate. The maximally tolerated dose (MTD) was reached in this study.

5.2 Study 4101- Rats

- The Cox's test for linear trend is not significant for either sex. The Cox's test for Departure from linear Trend is statistically significant at 0.05 level of significance for rats of either sex. That is, the effect of dose on mortality is not linear in dose.
- Tumor data analysis does not show any statistically significant positive linear trend in male rats. However, for female rats, cervix sarcoma tumor trend test indicated statistically significant difference between "high" dose galantamine and control. This contradicts the sponsor's conclusions shown on page 9 of this review.
- According to the Haseman's (1984) criterion, the study design is adequate. The maximally tolerated dose (MTD) was reached in both male and female rats of the medium and high dosage groups.

**6. References**

Chu, Cueto and Ward (1981). "Factors in the evaluation of 200 national cancer institute carcinogen bioassay." Journal of Toxicology and Enivironmental Health, Vol. 8, pp. 251-280.

Haseman, JK (1984). Statistical issues in the design, analysis and interpretation of animal carcinogenicity studies, environmental health perspectives, Vol. 58, pp 385-392.

Lin KK, and Ali MW (1995). Statistical review and evaluation of animal tumorigenicity studies. In: Statistics in the Pharmaceutical Industry, Second Edition, Revised and Expanded (Buncher CR, Tsay JY, Eds). Marcel Dekkers, New York, pp 19-57.

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HFD-710 / Dr. Koti
HFD-710 / Chron

## 7. Appendix

Figure A.1: Study 4199

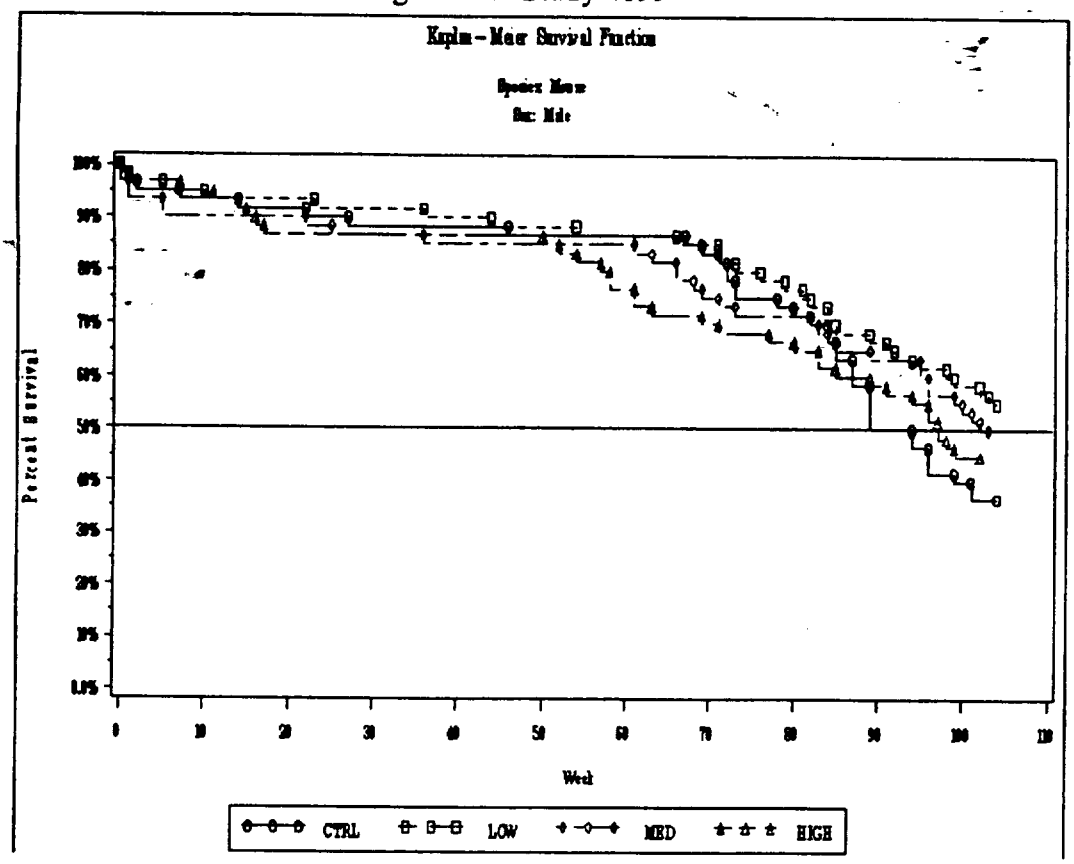


Figure A.2: Study 4199

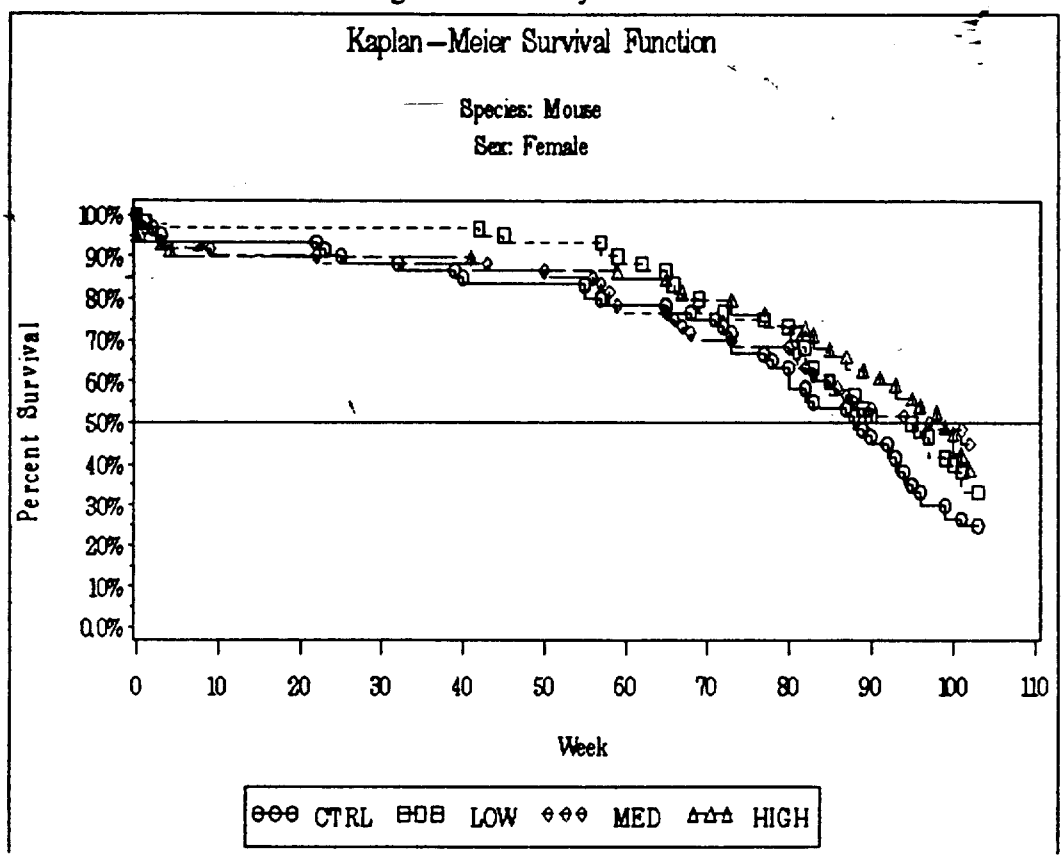


Figure A.3: Study 4101

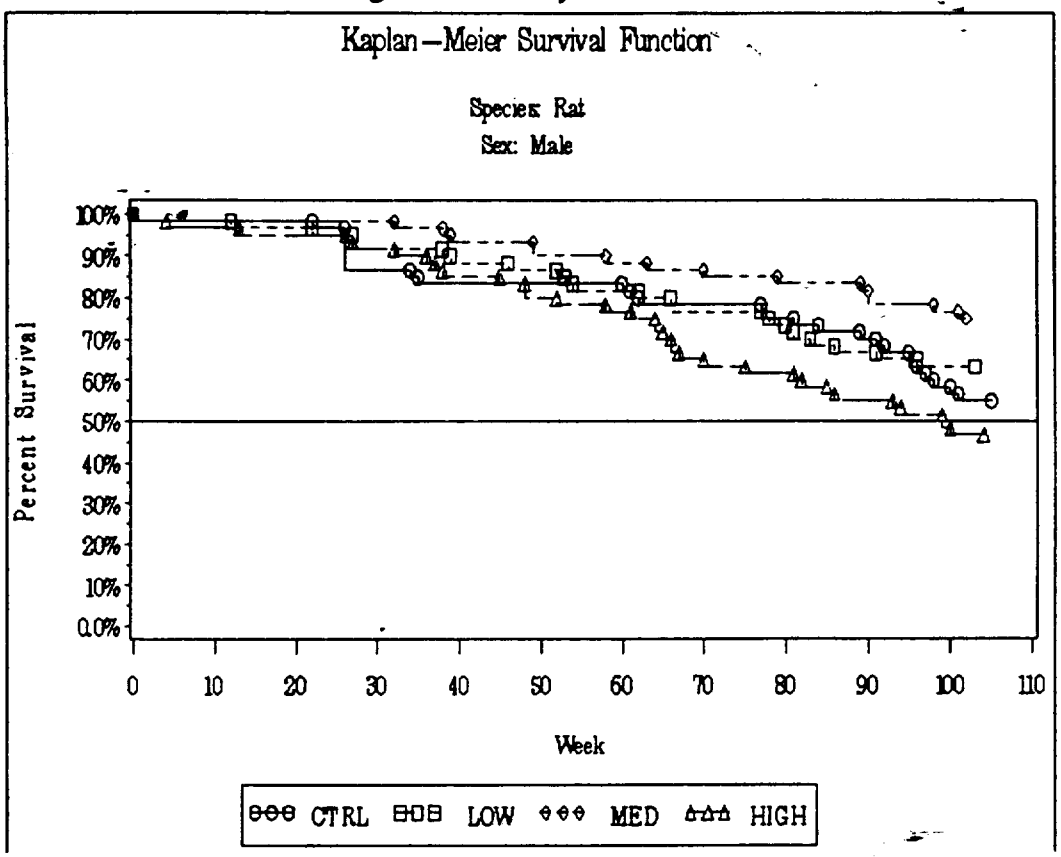
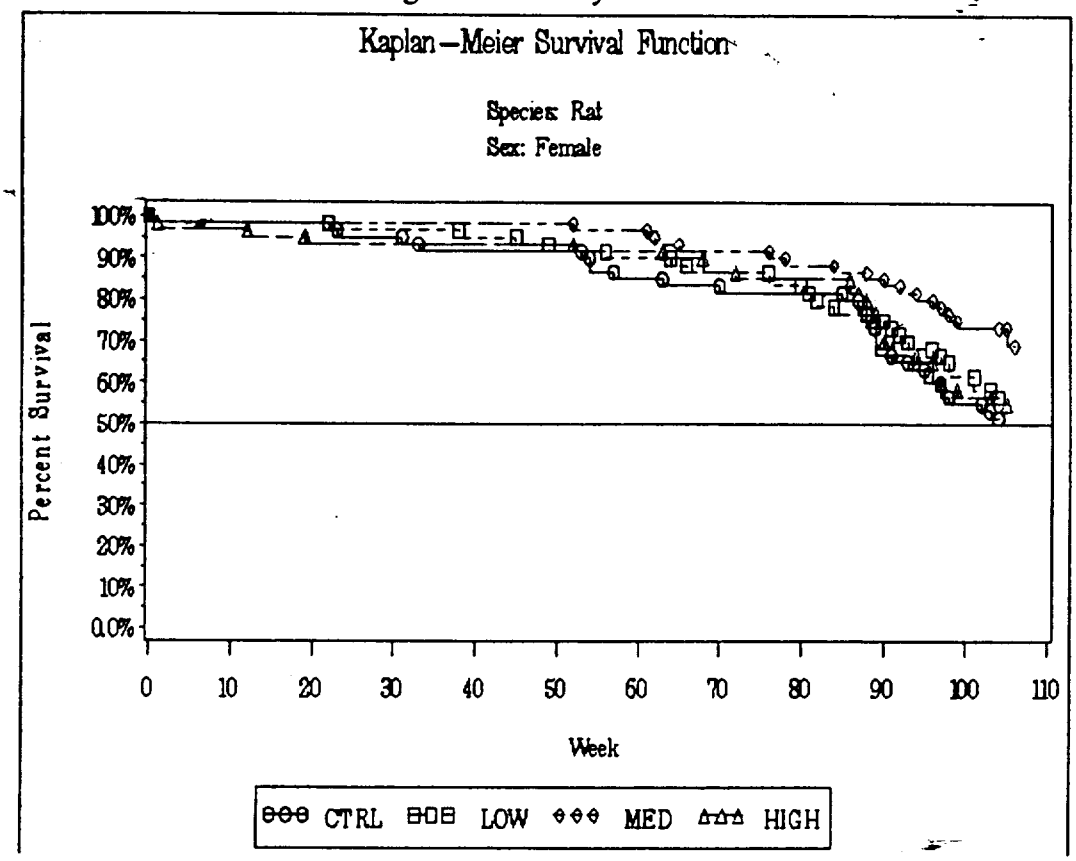


Figure A.4: Study 4101



## Table A.1 : Study 4199- Male Mice

| OrganName | OrganCode | TumorName | TumorCode | ExactPVvalue | AsympPValue |
|---|---|---|---|---|---|
| Pituitarygland | E1 | Adenoma | 4 | 0.6549 | 0.6540 |
| Adrenalglands | E3 | Adenoma,cortical | 462 | 1.0000 | 0.9714 |
| Kidneys | U1 | Adenoma,tubular | 418 | 0.6691 | 0.6710 |
| Pancreas | P | Endocrineadenoma | 493 | 1.0000 | 0.8771 |
| Thyroidglands | E4 | Follicularadenoma | 451 | 0.4957 | 0.4579 |
| Testes | G11 | Hemangioma | MV1 | 0.5927 | 0.6024 |
| Liver | L1 | Hemangioma | MV1 | 0.7589 | 0.7428 |
| Bonemarrow | H83 | Hemangioma | MV1 | 1.0000 | 0.9207 |
| Spleen | H1 | Hemangioma | MV1 | 1.0000 | 0.9207 |
| Skeletalmuscle,psoas | M611 | Hemangiosarcoma | MV2 | 0.7472 | 0.7292 |
| Spleen | H1 | Hemangiosarcoma | MV2 | 0.9563 | 0.9258 |
| Liver | L1 | Hepatocarcinoma | L2 | 0.7622 | 0.7509 |
| Liver | L1 | Hepatocellularadenom | L1 | 0.9454 | 0.9397 |
| Hematopoieticsystem | H4 | Histiocyticsarcoma | H62 | 0.9351 | 0.9057 |
| Testes | G11 | Leydigcelltumor,beni | ML1 | 0.7809 | 0.7657 |
| Hematopoieticsystem | H4 | Lymphoidleukemia | H12 | 0.9323 | 0.8922 |
| Hematopoieticsystem | H4 | Lymphoma,benign | H16 | 0.8036 | 0.7589 |
| Hematopoieticsystem | H4 | Lymphoma,malignant | H11 | 0.8429 | 0.8244 |
| Brain | N1 | Meningioma,malignant | Z84 | 0.7846 | 0.7466 |
| Hematopoieticsystem | H4 | Myeloidleukemia | H21 | 0.2444 | 0.0802 |
| Softtissue | M8 | Neurofibrosarcoma | Z53 | 1.0000 | 0.9207 |
| Mouth | D11 | Papilloma | 21 | 0.8036 | 0.7589 |
| Adrenalglands | E3 | Phaeochromocytoma,be | Z91 | 0.5089 | 0.4985 |
| Lungs | R2 | Primarylungtumor,ade | R1 | 0.7702 | 0.7613 |
| Testes | G11 | Schwannoma,benign | Z511 | 0.7500 | 0.7671 |

## Table A.2 : Study 4199- Female Mice

| OrganName | OrganCode | TumorName | TumorCode | ExactPVvalue | AsympPValue |
|---|---|---|---|---|---|
| Adrenalglands | E3 | Phaeochromocytoma,be | Z91 | 0.4387 | 0.4015 |
| Bone | M1 | Osteoma | M91 | 0.5177 | 0.5117 |
| Bone | M1 | Osteosarcoma | M93 | 0.2711 | 0.0930 |
| Bonemarrow | H83 | Hemangioma | MV1 | 0.3095 | 0.1035 |
| Cervix | G34 | Fibroleiomyoma | M72 | 0.8263 | 0.8087 |
| Ear | O2 | Chondrosarcoma | M84 | 0.2711 | 0.0930 |
| Hematopoieticsystem | H4 | Erythroleukemia | H25 | 0.4923 | 0.4903 |
| Hematopoieticsystem | H4 | Histiocyticsarcoma | H62 | 0.6306 | 0.6190 |
| Hematopoieticsystem | H4 | Lymphoidleukemia | H12 | 0.6098 | 0.5917 |
| Hematopoieticsystem | H4 | Lymphoma,malignant | H11 | 0.8411 | 0.8283 |
| Hematopoieticsystem | H4 | Myeloidleukemia | H21 | 0.9670 | 0.9350 |
| Lacrimalgland | O13 | Adenoma,papillary | 415 | 0.9559 | 0.9152 |

| | | | | | |
|---|---|---|---|---|---|
| Liver | L1 | Hemangioma | MV1 | 0.8411 | 0.8212 |
| Liver | L1 | Hepatoblastoma | L3 | 1.0000 | 0.9228 |
| Liver | L1 | Hepatocarcinoma | L2 | 1.0000 | 0.8822 |
| Liver | L1 | Hepatocellularadenom | L1 | 0.9264 | 0.9131 |
| Lungs | R2 | Primarylungtumor,ade | R1 | 0.7191 | 0.7084 |
| Mammarygland | I2 | Adenoma,papillary | 415 | 1.0000 | 0.8907 |
| Ovaries | G31 | Adenoma,complex-mult | 412 | 0.4628 | 0.4355 |
| Ovaries | G31 | Adenoma,papillary | 415 | 0.8235 | 0.7913 |
| Ovaries | G31 | Adenoma,papillarycys | 491 | 0.2989 | 0.2754 |
| Ovaries | G31 | Adenoma,tubular | 418 | 1.0000 | 0.8987 |
| Ovaries | G31 | Granulosa-thecacellt | G43 | 0.5882 | 0.5428 |
| Ovaries | G31 | Sertolicelltumor,ben | G21 | 0.2706 | 0.0969 |
| Oviduct | G32 | Fibroleiomyosarcoma | M74 | 0.4286 | 0.4849 |
| Pancreas | P | Endocrineadenoma | 493 | 0.2927 | 0.0949 |
| Pituitarygland | E1 | Adenoma | 4 | 0.8620 | 0.8437 |
| Smallintestine | D4 | Adenoma | 4 | 0.5882 | 0.5428 |
| Smallintestine | D4 | Hemangioendothelials | MV9 | 0.4318 | 0.4408 |
| Softtissue | M8 | Fibrohistiocytoma,be | M23 | 0.2844 | 0.1016 |
| Softtissue | M8 | Hemangiosarcoma | MV2 | 0.8509 | 0.8220 |
| Softtissue | M8 | Sarcoma | M61 | 0.7329 | 0.7119 |
| Softtissue | M8 | Schwannoma,benign | Z511 | 0.5882 | 0.5428 |
| Spleen | H1 | Hemangioma | MV1 | 1.0000 | 0.8907 |
| Thyroidglands | E4 | Follicularadenoma | 451 | 0.5686 | 0.5211 |
| Urinarybladder | U3 | Papilloma,transition | 23 | 0.8235 | 0.7913 |
| Urinarybladder | U3 | Sarcoma | M61 | 1.0000 | 0.9350 |
| Uterus | G33 | Adenocarcinoma | 6 | 0.3668 | 0.3184 |
| Uterus | G33 | Carcinoma | 8 | 1.0000 | 0.9294 |
| Uterus | G33 | Fibroleiomyoma | M72 | 0.7242 | 0.7083 |
| Uterus | G33 | Fibroleiomyosarcoma | M74 | 0.6905 | 0.7171 |
| Uterus | G33 | Glandularpolyp | 423 | 1.0000 | 0.9638 |
| Uterus | G33 | Leiomyoma | M71 | 0.0662 | 0.0390 |
| Uterus | G33 | Myxofibroma | M22 | 0.8235 | 0.7913 |
| Uterus | G33 | Sarcoma,malignantstr | M614 | 0.9676 | 0.9359 |
| Uterus | G33 | Stromalpolyp | 422 | 0.8264 | 0.8142 |
| Vagina | G35 | Sarcoma | M61 | 1.0000 | 0.9163 |

# Table A.3 : Study 4101- Male Rats

| OrganName | OrganCode | TumorName | TumorCode | ExactPVvalue | AsympPValue |
|---|---|---|---|---|---|
| Adrenalglands | E3 | Phaeochromocytoma,be | Z91 | 0.9457 | 0.9340 |
| Adrenalglands | E3 | Phaeochromocytoma,ma | Z92 | 0.5034 | 0.5019 |
| Brain | N1 | Astrocytoma,benign | Z31 | 0.7655 | 0.7591 |
| Brain | N1 | Astrocytoma,malignan | Z33 | 0.7687 | 0.7602 |
| Epididymides | G12 | Mesothelioma,benign | MM1 | 1.0000 | 0.8255 |
| Externalear | O21 | Carcinoma,basalsquam | 872 | 0.5067 | 0.5031 |
| Externalear | O21 | Carcinoma,sebaceouss | 853 | 0.2073 | 0.0371 |
| Largeintestine,colon | D52 | Adenocarcinoma,polyp | 622 | 0.5034 | 0.5019 |
| Liver | L1 | Hepatocellularadenom | L1 | 0.6848 | 0.6900 |
| Liver,caudallobes | L13 | Hepatocellularadenom | L1 | 0.7655 | 0.7591 |
| Liver,medianlobe | L12 | Hepatocarcinoma | L2 | 0.5034 | 0.5019 |
| Lungs | R2 | Primarylungtumor,ade | R1 | 0.5034 | 0.5019 |
| Lungs | R2 | Primarylungtumor,car | R2 | 1.0000 | 0.8230 |
| Lymphnode(s),bronchi | H38 | Hemangiosarcoma | MV9 | 0.7655 | 0.7591 |
| Lymphnode(s),mesente | H39 | Hemangioma | MV8 | 0.4559 | 0.4525 |
| Lymphoidandhematopoi | H4 | Lymphoidleukemia | H12 | 0.5959 | 0.5439 |
| Lymphoidandhematopoi | H4 | Lymphosarcoma | H11 | 0.7126 | 0.7784 |
| Lymphoidandhematopoi | H4 | Thymoma,predominantl | H151 | 0.5034 | 0.5019 |
| Lymphoidandhematopoi | H4 | Thymoma,predominantl | H152 | 0.9845 | 0.9437 |
| Mouth | D11 | Carcinoma,squamousce | 871 | 0.2078 | 0.0374 |
| Pancreas | P | Adenocarcinoma,endoc | 663 | 1.0000 | 0.8255 |
| Pancreas | P | Adenoma,endocrine | 493 | 0.6520 | 0.6623 |
| Pancreas | P | Adenoma,endocrine-ex | 494 | 1.0000 | 0.8205 |
| Pancreas | P | Adenoma,exocrine | 492 | 0.7552 | 0.7372 |
| Parathyroidgland(s) | E5 | Adenoma | 4 | 0.4965 | 0.4934 |
| Pituitarygland | E1 | Adenoma | 4 | 0.9293 | 0.9242 |
| Pituitarygland,parsd | E12 | Adenoma | 4 | 0.4448 | 0.4895 |
| Pituitarygland,parsi | E11 | Adenoma | 4 | 0.9625 | 0.9009 |
| Prostate | G21 | Adenoma,papillary | 415 | 1.0000 | 0.8255 |
| Salivarygland,paroti | S11 | Adenocarcinoma | 6 | 0.1931 | 0.0316 |
| Seminalvesicles | G22 | Carcinoma,scirrhous | 832 | 0.7059 | 0.7386 |
| Skin(abdomen) | I15 | Papilloma,squamousce | 25 | 0.5034 | 0.5019 |
| Skin(foreleg) | I17 | Papilloma,squamousce | 25 | 0.5034 | 0.5019 |
| Softtissue | M8 | Fibrohistiocyticsarc | M241 | 1.0000 | 0.8255 |
| Softtissue | M8 | Fibroma | M21 | 0.2602 | 0.2015 |
| Softtissue | M8 | Fibrosarcoma | M240 | 0.2199 | 0.0419 |
| Softtissue | M8 | Hemangioma | MV8 | 1.0000 | 0.8255 |
| Softtissue | M8 | Lipoma | M11 | 0.7655 | 0.7591 |
| Stomach,forestomach | D31 | Sarcoma | M61 | 0.4945 | 0.5086 |
| Testes | G11 | Leydigcelltumor,beni | ML1 | 0.5186 | 0.5358 |
| Testes | G11 | Mesothelioma,benign | MM1 | 1.0000 | 0.8205 |
| Thyroidglands | E4 | C-celladenoma | E4 | 0.7774 | 0.7830 |
| Thyroidglands | E4 | C-cellcarcinoma | E8 | 0.1931 | 0.0316 |

| | | | | | |
|---|---|---|---|---|---|
| Thyroidglands | E4 | Follicularadenocarci | 632 | 0.9174 | 0.8928 |
| Thyroidglands | E4 | Follicularadenoma | 451 | 0.7624 | 0.7648 |
| Urinarybladder | U3 | Papilloma,transition | 23 | 1.0000 | 0.8312 |

## Table A.4: Study 4101- Female Rats

| OrganName | OrganCode | TumorName | TumorCode | ExactPVvalue | AsympPValue |
|---|---|---|---|---|---|
| Adrenalglands | E3 | Phaeochromocytoma,be | Z91 | 0.7832 | 0.7804 |
| Adrenalglands | E3 | Phaeochromocytoma,ma | Z92 | 0.2557 | 0.0573 |
| Bone | M1 | Osteosarcoma | M93 | 0.7596 | 0.7714 |
| Brain | N1 | Granularcelltumor,be | Z41 | 0.7383 | 0.7442 |
| Brain | N1 | Meningioma,benign | Z81 | 0.7832 | 0.7804 |
| Brain | N1 | Oligodendroglioma,be | Z32 | 0.5455 | 0.5456 |
| Cervix | G34 | Carcinoma,adenosquam | 873 | 0.0604 | 0.0103 |
| Cervix | G34 | Carcinoma,squamousce | 871 | 1.0000 | 0.8397 |
| Cervix | G34 | Sarcoma | M61 | 0.0143 | 0.0021 |
| Externalear | O21 | Carcinoma,sebaceouss | 853 | 0.2500 | 0.0550 |
| Kidneys | U1 | Carcinoma,transition | 861 | 0.9259 | 0.8765 |
| Liver | L1 | Hepatocarcinoma | L2 | 0.7817 | 0.7784 |
| Liver | L1 | Hepatocellularadenom | L1 | 0.1860 | 0.1389 |
| Lymphnode(s),mesente | H39 | Hemangioma | MV8 | 0.5134 | 0.5523 |
| Lymphoidandhematopoi | H4 | Thymoma,predominantl | H151 | 0.5455 | 0.5456 |
| Lymphoidandhematopoi | H4 | Thymoma,predominantl | H152 | 0.4059 | 0.3960 |
| Mammarygland | I2 | Adenocarcinoma | 6 | 0.8505 | 0.8446 |
| Mammarygland | I2 | Adenocarcinoma,papil | 625 | 1.0000 | 0.8223 |
| Mammarygland | I2 | Adenofibroma | 442 | 0.3438 | 0.0940 |
| Mammarygland | I2 | Fibroadenoma | 441 | 1.0000 | 0.8007 |
| Mammarygland(abdomin | I23 | Adenocarcinoma | 6 | 0.7914 | 0.7721 |
| Mammarygland(abdomin | I23 | Adenofibroma | 442 | 0.7660 | 0.7739 |
| Mammarygland(abdomin | I23 | Fibroadenoma | 441 | 0.8806 | 0.8756 |
| Mammarygland(abdomin | I23 | Fibroma | M21 | 0.3165 | 0.2585 |
| Mammarygland(inguina | I24 | Adenocarcinoma | 6 | 0.3068 | 0.3237 |
| Mammarygland(inguina | I24 | Adenoma,acinar | 411 | 1.0000 | 0.8397 |
| Mammarygland(inguina | I24 | Fibroadenoma | 441 | 0.8546 | 0.8519 |
| Mammarygland(neckreg | I21 | Adenocarcinoma | 6 | 1.0000 | 0.8397 |
| Mammarygland(neckreg | I21 | Fibroadenoma | 441 | 0.7114 | 0.7424 |
| Mammarygland(thoraci | I22 | Adenocarcinoma | 6 | 0.9850 | 0.9703 |
| Mammarygland(thoraci | I22 | Fibroadenoma | 441 | 0.7722 | 0.7818 |
| Nose | R11 | Carcinoma,adenosquam | 873 | 0.7800 | 0.7761 |
| Ovaries | G31 | Adenoma | 4 | 1.0000 | 0.8397 |
| Ovaries | G31 | Granulosa-thecacellt | G44 | 0.1042 | 0.0653 |
| Pancreas | P | Adenoma,endocrine | 493 | 0.8385 | 0.8702 |
| Pituitarygland | E1 | Adenoma | 4 | 1.0000 | 1.0000 |
| Pituitarygland,parsd | E12 | Adenoma | 4 | 0.3165 | 0.2585 |
| Pituitarygland,parsi | E11 | Adenoma | 4 | 0.7832 | 0.7804 |

| | | | | | |
|---|---|---|---|---|---|
| Skin(flank) | I14 | Kerato-acanthoma | 32 | 0.7832 | 0.7804 |
| Skin(head) | I11 | Carcinoma,squamousce | 871 | 0.5158 | 0.5457 |
| Softtissue | M8 | Sarcoma | M61 | 0.2500 | 0.0550 |
| Thyroidglands | E4 | C-celladenoma | E4 | 0.5131 | 0.5236 |
| Thyroidglands | E4 | C-cellcarcinoma | E8 | 0.7383 | 0.7442 |
| Thyroidglands | E4 | Follicularadenoma | 451 | 0.9018 | 0.8959 |
| Uterus | G33 | Adenocarcinoma | 6 | 0.0201 | 0.0155 |
| Uterus | G33 | Adenocarcinoma,papil | 625 | 0.5045 | 0.5449 |
| Uterus | G33 | Adenocarcinoma,polyp | 622 | 1.0000 | 0.8397 |
| Uterus | G33 | Adenoma,papillary | 415 | 0.5118 | 0.5401 |
| Uterus | G33 | Carcinoma | 8 | 1.0000 | 0.8326 |
| Uterus | G33 | Carcinoma,adenosquam | 873 | 1.0000 | 0.8049 |
| Uterus | G33 | Carcinoma,poorlydiff | 891 | 0.5161 | 0.5458 |
| Uterus | G33 | Carcinoma,squamousce | 871 | 0.7273 | 0.7385 |
| Uterus | G33 | Fibrosarcoma | M240 | 1.0000 | 0.8397 |
| Uterus | G33 | Polyp,glandular | 423 | 0.2026 | 0.1323 |
| Uterus | G33 | Polyp,stromal | 422 | 0.5522 | 0.5567 |
| Uterus | G33 | Sarcoma | M61 | 0.1946 | 0.1349 |
| Vagina | G35 | Polyp,stromal | 422 | 0.5134 | 0.5523 |
| Vagina | G35 | Sarcoma | M61 | 0.5240 | 0.5665 |